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Canadian Psychiatric Association Journal

Volume 4
Special Supplement

1959

McGill University Conference on Depression and Allied States

Montreal
March 19-21, 1959

La Revue de l'Association Canadienne de Psychiatrie

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The Canadian Psychiatric Association Journal has issued this Special Supplement to bring to its readers the proceedings of the Conference on Depression and Allied States held in Montreal on March 19-21, 1959. The Conference was sponsored by the Department of Psychiatry of McGill University, Montreal, for the purpose of examining problems of psychiatric depression in the light of recent advances in therapy.

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PSYCHIATRIC CONCEPTS OF DEPRESSION: NOMENCLATURE AND CLASSIFICATION

H. E. LEHMANN*

In psychiatric usage the term depression has three different meanings: it refers to a symptom, to a syndrome, and to a nosological entity. A similar situation exists in regard to anxiety. Almost fifty years ago Abraham (1) wrote that anxiety and depression are related to each other in the same way as are fear and grief. The different meanings of anxiety, however, have been more extensively studied and they are better understood and more clearly defined than the various psychiatric aspects of depression. A brief comparison of experimental behavioural data obtained for these two conditions may be in place here.

Experimental findings in anxiety and depression

The experimental investigation of anxiety has suggested the existence of multiple factors resulting in the behavioural anxiety response, namely a specific avoidance factor and an unspecific arousal factor (2), each factor capable of being influenced independently. The different effects of acute and chronic anxiety (3) or of experimentally induced stress and personality-inherent anxiety (4) have been investigated and the interesting fact has been established that anxiety of moderate intensity can facilitate the learning of certain tasks (5).

In contrast to this, there is general agreement among clinicians and experimental workers that depression in the psychiatric sense never facilitates learning or behavioural responses but is always characterized by inhibition of psychic processes (6, 7).

Experimental psychologists are widely committed to research on anxiety responses in animals. Considering animals as analogues of the human organism they can give operational definitions of anxiety. One experimental paradigm for anxiety defines it as the disorganizing effect of anticipated pain on a previously established response pattern (8). This is a fair approximation to the general concept of threat which is usually considered to be the factor giving rise to fear and anxiety reactions in man.

The natural paradigms of depression

On the other hand, virtually no experimental animal data on depressive states are available because no experimental model exists at present for depressive states in animals, at least not for depressive states that a psychiatrist would accept as analogues to the psychiatric concept of depression. There are, however, natural paradigms of depression in animals well known to all who have observed animals closely. These are the reactive depressions which occur in some animals after the loss of their master or mate. Such animal depressions bear an almost uncanny resemblance to human depressive states not only in their general behavioural pattern but also with regard to the principal etiological factor involved, namely, loss of a love object. They lead us in certain instances even to infer that dynamic factors like conflict and guilt might be responsible for specific self-punitive behaviour of depressed animals (9).

There is also a dearth of research data on experimentally induced depressions in human subjects because depressive states do not lend themselves to laboratory experiments as easily as anxiety states which can be induced with fair regularity by the impact of various physiological, pharmacological and psychological factors. Hypnosis (10) has so far been the most reliable means of creating the complex basic conditions for an experimental study of depressive states in humans since

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neither drugs nor other physical agents or conditions will induce a depressive syndrome in man with sufficient regularity. But in humans, too, we find a condition which might be called the natural paradigm of depression, namely the anaclitic depressions of infants following the separation from their mother which have been so convincingly demonstrated by Spitz (11).

Definition of the depressive syndrome

Pavlovian Russian psychiatry speaks of the affective psychoses as disturbances of the first signalling system. Tentative operational definitions of experimental anxiety can be proposed because the key factors of anxiety are pain and security and as such they are directly given as potential experiences of the individual per se. Any operational definition of depression, however, has so far proved unworkable because the loss of a love object already presupposes the existence of a relationship transcending the individual.

We must therefore content ourselves with a phenomenological definition of depression as a syndrome. Fortunately, there has always been agreement among clinicians about the phenomena that characterize the psychiatric condition which we call depression or sometimes melancholia. The characteristic symptoms are: a sad, despairing mood; decrease of mental productivity and reduction of drive; retardation or agitation in the field of expressive motor responses. These might be called the primary symptoms of depression. There are often also secondary symptoms, particularly in states of severe or pathological depression. The group of secondary symptoms comprises: feelings of hopelessness; hypochondriacal preoccupation; feelings of depersonalization; obsessive-compulsive behaviour; ideas of self-accusation and self-depreciation; nihilistic delusions; paranoid delusions; hallucinations; suicidal ruminations and tendencies. Insomnia, anorexia and weight loss are usually associated with depressive states, and various autonomic, metabolic and endocrine abnormalities might be present.

The secondary symptoms of depression are less regularly found than the primary, and among the primary symptoms, the sad, despairing emotional state and the depressive mood seem to constitute the real core of all depressions in which the psychiatrist is interested.

Pathophysiological observations

Every emotional state is represented by its associated autonomic responses, its expressive physiognomic motor components and the personal, private, inner experience of the individual. Although there exists now a considerable body of information on biochemical, metabolic (12), endocrine (13, 14, 15), autonomic (16) and neurophysiological (17) phenomena found in depressive states, it can be stated that no unequivocal and consistent test findings on the basic science level have been demonstrated to date as regular and specific signs of depressions. Strongin and Hinsie (16) reported that they could diagnose manic-depressive psychosis in a group of undifferentiated depressed patients quite reliably on the basis of reduced parotid secretion, and Shagass (17) feels that his sedation threshold distinguishes effectively between endogenous and reactive depression, but the clinical value of these tests procedures is quite limited. Observation, interview and history are simpler and more reliable tools of differential diagnosis. We cannot yet make an objective psychiatric diagnosis of depression.

It is noteworthy that some of the physical functions studied in depression are increased rather than decreased. Blood pressure and pulse rate, adrenal and thyroid activity (15) and cerebral resistance to inhibiting drugs (17) are frequently elevated in depressed patients. The adrenal function is so regularly increased in depressive states that we have proposed to use this heightened state of adrenal functioning as

a clinical indicator of the depth of depression. In one intriguing case we were able to observe the reflection of psychodynamic shifts in the patient's psychic organization through following her eosinophil count. Whenever this depressed woman expressed ideas of unworthiness and self-accusation, her eosinophil count was low as an indication of increased adrenal activity, but on days when she employed restitutive psychological defenses and expressed paranoid delusions projecting the blame on to others, her eosinophil count rose sharply, signalling a lowering of adrenal activity (14). It is possible that the stimulation of certain physical functions in depressive states is merely reflecting the admixture of an anxiety component, but at our state of knowledge it is extremely difficult and sometimes impossible to differentiate between "pure depression" and anxiety and it is questionable whether depression without a certain degree of anxiety really exists.

Funkenstein (18), who demonstrated an endocrine reaction pattern which allows a distinction to be made between anxiety and aggression in human subjects under stress, has recently included depressive reactions with anxiety in the stress pattern resulting in epinephrine discharge. The precise differentiation between depression and anxiety remains an academic nicety. On the other hand, to establish the relative proportion of depression and anxiety and also the priority of one or the other is important for the clinician since the therapeutic management of depression and anxiety is quite different on the physical as well as on the psychotherapeutic level. For example, in a patient who is primarily anxious and has become depressed only as a secondary reaction, electroconvulsive therapy may increase the anxiety and make the patient worse as regards his total functioning, while the same therapy by reducing a primary depression will also reduce anxiety if it was a secondary symptom.

Differential diagnosis of depressive states

Whatever accounts for the inconsistent autonomic and metabolic findings, we must base our diagnosis of a depressive syndrome on the behavioural manifestations and the verbal reports of our patients. Most depressions are probably diagnosed by inspection, because the physiognomic features of the depressive countenance are so typical, so well known and such sensitive indicators. Sometimes, however, the patient's appearance is deceiving and our diagnosis then depends entirely on the evaluation of a single symptom, which is possibly the most essential of all, namely, the patient's verbal description of his mood and his feelings. Additional information about hereditary background, somatotype, age, premorbid personality structure, history of previous illness and events immediately preceding the depression is often helpful in arriving at a differential diagnosis of the nosological category once the depressive syndrome has been recognized.

Normal and pathological depressions

In classifying depressive states the first distinction to be made is between normal and pathological reactions. Mourning and grief reactions in general are normal reactions to the loss of a love object—this may be another person, money, the depressed individual's prestige, his cherished hopes, his health—and it is not always possible to distinguish such normal grief reactions from pathological depressions on phenomenological grounds alone. A depression is judged to be pathological if there is insufficient specific cause for it in the patient's immediate past, if it lasts too long, or if its symptoms are too severe. Clearly, the difference between normal and pathological depression is only one of degree in many cases. Nor is it always possible to make a clear-cut distinction between endogenous depressions which by definition are not caused by any external life situations and exogenous depressions which more frequently are called reactive, psychogenic or neurotic

depressions and occur as a reaction to traumatic events. In many cases a typical endogenous depression is precipitated by a stressful situation, and the distinction between causal and merely precipitating factors is sometimes a rather arbitrary issue.

Endogenous and reactive depressions

This is not to say that the differentiation between endogenous and reactive depression is not a valid one. On the contrary, such differential diagnosis is of considerable value for purposes of therapy and prognosis. There are, however, cases where no clear decision can be reached in the diagnostic weighing of endogenous and reactive components of a given depressive syndrome. Numerous schemes have been proposed for the distinction between endogenous and reactive depressions with different symptoms serving as the criteria. Such symptomatic differentiation between endogenous and reactive depressions is often more successful than between normal and pathological depression, yet a reliable diagnosis can only be made when all available information beyond the given symptomatology is fully considered.

Many psychiatrists insist that patients suffering from reactive depressions do not express severe self-accusations and that they respond temporarily to reassurance and support, which is supposed to be in contrast to patients with endogenous depressions. Yet, during the last two years we have seen a number of depressed patients who had been victims of Nazi persecution in concentration camps 15 years ago and developed reactive depressions. These tragic individuals, having reacted to traumatic stresses of unparalleled power, do not resemble the ordinary patient with a reactive depression but often present all the symptoms of an endogenous depression including severe self-accusations and refractoriness to supportive measures.

Manic-depressive psychosis and involutional melancholia

Two major classifications are generally recognized within the group of endogenous depressions: manic-depressive psychosis and involutional melancholia. Again it must be stressed that a reliable differential diagnosis between these two nosological entities cannot be based entirely on the observation of symptoms. Certain features like agitation and hypochondriasis are more frequently observed in involutional melancholia than in manic-depressive psychosis but this is only a relative finding and many manic-depressive patients in the depressed phase are also agitated and hypochondriacal while involutional depression might manifest itself with retardation and self-accusation.

It should be noted that Kraepelin, after describing involutional melancholia as an entity, later reversed his attitude and classified all endogenous depressions as manic-depressive manifestations. In some psychiatric centres, in Germany for instance, involutional melancholia is seldom if ever diagnosed. However, in many parts of the world it is recognized as a separate diagnostic entity and the official classifications of psychiatric diagnoses issued by the World Health Organization (19) and the American Psychiatric Association (20) both include it, although the latter refers to it as involutional psychosis. From the genetic point of view, Kallmann (21) has shown that involutional melancholia is related more to schizophrenia than to manic-depressive psychosis. The premorbid personality of most patients suffering from involutional melancholia is quite different from that which is found in patients prior to a manic-depressive illness. The predominance of the pyknic or mesomorphic somatotype which is now generally recognized in the manic-depressive group is not found among patients with involutional melancholia. While all this is supporting evidence for those who refuse to subsume endogenous depressive states

occurring for the first time at the involutional age under the general heading of manic-depressive psychosis, we have as yet no direct evidence that involutional melancholia is an independent nosological entity. It is possible that a number of cases so diagnosed represent an atypical form of late schizophrenia.

In many cases, the correct differential diagnosis between involutional melancholia and manic-depressive psychosis can only be made years after the event; that is, after a patient who at first had been diagnosed as suffering from involutional melancholia because there was no history of a previous attack is seen again some time later presenting an entirely new set of depressive or manic symptoms. In this case, as we have often done, one would alter the original diagnosis of involutional melancholia in retrospect since involutional melancholia by definition does not recur nor will a patient so diagnosed ever present manic symptoms.

Diagnostic sub-groupings

The classification of pathological depressions establishing the three major nosological entities of manic-depressive psychosis, involutional melancholia, and reactive depression would not be complete without considering the nomenclature of various diagnostic subgroupings. The term 'psychotic depression' (20) is sometimes used to designate a depressive state associated with severe behaviour disorder or disturbed contact with reality. In this connection, it should be noted that a severe reactive depression may attain psychotic degrees of personality disintegration, so that the term 'psychotic depression' will not always differentiate between endogenous or reactive depression. The diagnosis 'recurrent depression' is more a clinically descriptive term than a diagnosis in the sense of referring to a nosological entity. Recurrent depressions may be endogenous or reactive. Many composite expressions are used to designate depressive syndromes occurring in other psychiatric conditions. One sometimes reads of alcoholic depressions or schizophrenic depressions or senile depressions. These terms, while valuable for their descriptive contribution, cannot be considered as independent psychiatric diagnoses since the depressive syndrome in these conditions is not a primary manifestation.

If one assumes that there is a primary morbid condition which expresses itself in the form of a depressive syndrome, one postulates that there is some kind of physical substrate of the depressive syndrome. This physical substrate may well respond to psychological as well as to physical interference, and the fact that depressive states may respond to psychotherapy as well as to electroconvulsive treatment or to drugs does not constitute an argument against this hypothesis.

Psychoanalytic and existential concepts

Psychoanalysts have made valuable contributions to our understanding of all depressions, the normal as well as the pathological, by elucidating the basic dynamic processes involved in mourning, grief and pathological depressions. The mechanism of introjection, that is, of the incorporation of an object towards which one has an ambivalent relationship, namely love and hate simultaneously, seems to be operating in most depressive syndromes. Existential analysis of the depressive syndrome has brought out the radical change of the depressed person's experience of his world in its spatial and temporal categoriality. Such dynamic analysis is helpful in rendering the depressed person's feelings and behaviour understandable, but it is not a practical means for making a clinical diagnosis or for classifying depressive syndromes.

Diagnostic approaches

One cannot rely on the demonstration of introjection and fixation at the oral libidinal level or on the radical change of the 'vital experiencing' (K. Schneider) if one attempts to classify the major depressions within a consistent conceptual frame-

work. In summary, the following approaches are adopted by psychiatrists when attempting to make a differential diagnosis of a pathological depression:

1. The phenomenological approach (the presence of retardation or agitation, of diurnal fluctuations, hypochondriasis, self-blame, etc.).
2. The etiological approach (psychogenic or endogenous).
3. The somatotypological approach (pyknic or mesomorphic vs. other somatotypes).
4. The consideration of the premorbid personality (outgoing plastic vs. restrained rigid personality structure).
5. The evaluation of the natural history of the disease (duration and periodicity).
6. The impairment of certain autonomic functions (parotid secretion).
7. The study of neuropharmacological response patterns (sedation threshold).

Historical development of the psychiatric concept of depression*

Historically, we find the first clinical descriptions of depressive states or melancholia in Hippocrates' writings in the fourth century B.C. Aretaeus, a physician living in the first century A.D., had already noted that melancholia seemed to be a modification of mania and did not affect the intellectual faculties. He described the listless, sad, hopeless countenance of the victims of melancholia who "become thin by their own agitation . . . complain of a thousand futilities and desire death." Many centuries later, in 1667, the French mathematician and philosopher, Jean Baptist Denis, made bold advances in therapy when he produced a remission in a man suffering from reactive depression with two transfusions of calves' blood. While we may marvel at the circumstances that led the patient to survive this kind of shock therapy (the patient died only after a third transfusion), we should also note the recorded differential diagnosis, i.e. a distinction between melancholia, long thought to be due to morbid humors, and a reactive depression due in this case to disappointment in love. The Greeks, the Romans, and European medicine in general up to the nineteenth century considered love a most important psychogenic cause of depression. Boerhaave, in 1735, described the intellectual inhibition of the depressive person when he pointed out that the melancholic patient is "always intent upon one and the same thought." In 1777, Cullen refers to states of depression as states of collapse. This was the period when the physiological notions of excitability and exhaustion of the nervous system were first finding wide acclaim among physicians. It was also the time when Cheyne spoke of melancholia as "the English malady." By the end of the eighteenth century, a growing interest in classification was becoming apparent and, as Zilboorg and Henry (22) point out, "finally led the psychiatrist to consider almost every symptom as indicative of a separate disease." Erhard, in 1796, for instance, distinguishes between melancholia hypochondriaca, melancholia thanatophobia and melancholia demonomania. Psychiatry was coming close to its present ways of classifying depressive states when Falret in 1854 published his work on "la folie circulaire" or "folie à double forme" which refers, of course, to the subject of manic-depressive psychosis by another name. The expression manic-depressive psychosis is first used by Kraepelin in 1899 (22). In 1904, Adolf Meyer proposed to substitute the term depression for melancholia (23) and in 1907, Kraepelin was reluctantly convinced by Dreyfus (22) that involutional melancholia was not an independent entity. Freud's classical paper on Mourning and Melancholia (24) was published in 1917 and Abraham (25) in 1924 published his fundamental research on the dynamics of manic-depressive psychosis.

*Much of the historical information contained in this part of the paper was obtained from Zilboorg and Henry (22).

The major framework for the classification and for the psychodynamic structure of depressive states in psychiatry had been established. The breakthrough in the treatment of pathological depressions came in the middle thirties with the introduction of convulsive therapy by Meduna and by Cerletti and Bini. All of us at this meeting are personally involved in the historical development of pharmacotherapy in depressions. In the whole complex problem of depressive states, only one great sector remains still *terra incognita*, that is, the pathophysiology of depressions.

Epidemiological observations

It is difficult to evaluate the changing trends in the incidence of depressions during the last fifty years. Kielholz (26) from the Psychiatric University Clinic in Basle, reports a steeply rising proportion of depressive manifestations in the yearly admissions to this psychiatric centre during the last ten years. On the other hand, an analysis of the incidence of depressive syndromes among admissions to the Verdun Protestant Hospital in Montreal between 1894 and 1958 clearly establishes a gradual decrease from 33 per cent of depressive conditions at the beginning of the century to 18 per cent of all admissions in 1958. Geographic and sociological factors may have operated in producing these different trends. The diagnosis of a depressive syndrome is probably less subject to changing fashions in classification than many other psychiatric conditions.

The type of culture and the extent of civilization existing in a given population seem to influence not only the ratio of depressive states to other psychiatric conditions but also the phenomenology of depressive syndromes. It has been observed, for instance, that the incidence of depressions among the Negroes of the northern United States, and the incidence of suicide among them, is considerably higher than among the Negroes of the South (23). Depressions are comparatively rare in primitive societies, for instance the Kenya natives and the Bantu (23). It is interesting to note that the symptomatology of depressive reactions in these preliterate societies is apparently characterized by a strong prevalence of hypochondriacal complaints and delusions, and an almost complete absence of self-accusations and guilt feelings. On the other hand, paranoid manifestations are commonly associated with pathological depressions in these primitive people. Such observations make it highly questionable whether guilt feelings and self-depreciation are really the focal and primary manifestations of psychiatric depressions that we consider them to be, or whether they are not superimposed products of our Greek-Hebrew-Christian culture which places so much emphasis on the responsibility of the individual.

Methodology of the concept of depression

This discussion would not be complete without a semantic analysis of the concept of depression. The term depression may be applied not only to different degrees of complexity within the same methodological category, for instance to a symptom, a syndrome, or a nosological entity, but it is also used widely on quite different methodological levels, namely, the psychological, the behavioural and the physiological. On the psychological-psychiatric level, the concept of depression is defined by the complex symptomatology which has been described, and it should be recalled that this psychiatric concept of depression might imply behavioural and biological excitation as well as inhibition in the patient's psychophysiological functioning. On the behavioural level, the concept of depression can be defined more concisely as a reduction of spontaneity, regardless of what causes or mechanisms have brought this about and regardless of the accompanying emotion. The third meaning of depression is applied to the physiological level where depression is clearly and operationally defined by the biologist who refers to depression whenever there is a primary reduction of a function.

The introduction of some of the new psychoactive drugs has caused a certain confusion among psychiatrists with regard to the term depression. Therapeutic effects of these drugs were sometimes looked for in psychiatric conditions which were called depressions but deserve this name only on the behavioural and not on the psychiatric level. However, on the behavioural level too, certain important distinctions must be made, and it is proposed to consider the following differentiation of depressed states on this level; that is, when only reduction of spontaneity is the criterion:

(*a*) Depression of the arousal system. This leads to conditions of coma, sopor and somnolence, and is primarily due to a physiological depression of certain cerebral functions.

(*b*) Asthenic depression. Phenomenologically, this type of depression is characterized by states of exhaustion and fatigue. Asthenic depression on the behavioural level is due to the physiological depression of metabolic and endocrine functions.

(*c*) Apathetic depression. This condition is characterized by a primary lack of drive and initiative, meaning that no physical cause for it can be demonstrated and that the apparent apathy cannot be understood as a psychological defense mechanism. Clinical examples of this state can be found in simple schizophrenia.

(*d*) Catatonic depression. Examples of this type of behavioural depression are found in affective and schizophrenic stupor and withdrawal, when these phenomena can be interpreted as restitutive symptoms and defense reactions.

(*e*) Dysphoric depression. This is depression in the true psychiatric sense. It must be dealt with on a new methodological level and is characterized by a specific phenomenological syndrome involving a complex system of excitations and inhibitions within the setting of the focal depressive mood.

Clarity of communication is a crucial issue for psychiatry. A psychiatric discussion of the biology, the phenomenology, the dynamics and the therapy of depressive states can avoid ambiguity only if it explicitly states on which methodological level it is conducted. Diagnostic classifications can be quickly learned but methodological distinctions must be clearly understood.

Résumé

En psychiatrie, le terme de "dépression" comporte trois significations: il se rapporte à un symptôme, à un syndrome et à une entité nosologique. Cependant, contrairement à la névrose d'angoisse qui a été étudiée de façon extensive par les psychologues expérimentaux, nous savons comparativement peu de choses sur la dépression, au point de vue de la symptomatologie expérimentale.

Les traits phénoménologiques essentiels qui caractérisent la dépression, sont un sentiment de tristesse et de désespérance, l'impossibilité d'un travail productif de la pensée ou de l'activité, un ralentissement ou une agitation au niveau de la sphère motrice. L'inhibition est le principal mécanisme psychologique mis en cause. Les traits dynamiques essentiels comprennent une introjection et une régression au stade oral (précédant le stade génital) du développement de la libido. Il paraît presque certain que, dans la dépression, un certain nombre de processus nerveux et endocriniens ne sont pas ralentis dans leur activité, mais fonctionnent au contraire à une cadence plus élevée que la normale.

Le diagnostic clinique repose pour une part considérable sur une impression visuelle que donne le patient, c'est-à-dire sur l'expression du visage, l'attitude, la mimique et sur le comportement général. La prédominance de l'inhibition restreint fréquemment l'expression verbale des sentiments, et notre connaissance des phénomènes autonomes, biochimiques et endocriniens est trop limitée, pour baser sur eux un diagnostic de dépression. En clinique, il importe de faire la distinction entre dépressions ordinaires et pathologiques, ainsi qu'entre dépressions endogènes,

exogènes ou psychoréactives, bien que le diagnostic différentiel soit parfois difficile. Les critères suivants ont été adoptés par les psychiatres pour différencier les diverses formes de dépression:

1° Critères phénoménologiques (fluctuations diurnes, agressivité dirigée vers le dedans ou vers le dehors, etc.).
2° Critères étiologiques (psychogène ou non psychogène).
3° Critères somato-typologiques (sujet picnique ou non, mésomorphique ou non).
4° Prise en considération de la personnalité prémorbide (personnalité expansive ou renfermée).
5° Appréciation de l'histoire de la maladie (durée et périodicité).
6° Dégradation de certaines fonctions autonomes (sécrétion des parotides).
7° Etude du mode de réponse aux agents neuro-pharmacologiques (seuil d'apparition de la sédation).

Au point de vue historique, Hippocrate fut le premier à décrire des états dépressifs, qu'il groupait sous le nom de mélancolie. En 1855, Falret désigna du nom de folie circulaire les états maniaques et dépressifs récidivant périodiquement. Kraepelin, en 1899, parle le premier de la psychose maniaco-dépressive comme d'une entité. Adolf Meyer propose, en 1904, de remplacer le terme de mélancolie par celui de dépression. En Europe, en Allemagne spécialement, d'importants centres psychiatriques demeurent sceptiques vis-à-vis du diagnostic de mélancolie involutive, et même le rejettent purement et simplement. En 1917, Freud fait paraître son étude classique sur la tristesse profonde et la mélancolie.

Le type de culture et le degré de civilisation d'une population donnée semble influencer la phénoménologie des états dépressifs, aussi bien que leur fréquence. Les cas, comparativement rares, qui ont été observés dans quelques communautés primitives d'Afrique, se caractérisaient par la prédominance des symptômes hypocondriaques et par l'absence quasi totale du symptôme d'auto-accusation.

Le terme de dépression peut être appliqué non seulement aux différents degrés de complexité d'une même catégorie méthodologique (symptôme—syndrome—entité diagnostique), mais aussi aux différents plans méthodologiques (physiologique, psychologique, comportement). Sur le plan psychologique et psychiatrique, la dépression se définit comme un complexe symptomatologique qui peut fréquemment comporter une inhibition, aussi bien qu'une excitation émotive, biologique, ou siégeant dans le comportement. Sur le plan physiologique, c'est en principe la réduction d'une fonction. Au point de vue du comportement, ce concept ne peut se définir que comme une diminution de la spontanéité (quelle qu'en soit la cause ou le mécanisme), sans que soit prise en considération l'émotion concomitante. Sous ce rapport, l'auteur propose de distinguer entre:

a) dépression de la vigilance (coma, somnolence);
b) dépression asthénique (épuisement, fatigue intense, insuffisance endocrinienne);
c) dépression apathique (défaut primaire d'impulsion et d'initiative, comme dans la schizophrénie simple);
d) dépression catatonique (stupeur affective ou schizophrénique, repli sur soi-même en tant que réaction de défense);
e) dépression psychiatrique (à placer sur un autre plan méthodologique, et englobant un système complexe d'excitations et d'inhibitions).

L'auteur propose que, dans les discussions concernant la biologie, la dynamique et la thérapeutique des états dépressifs, il soit toujours clairement précisé à quel plan méthodologique on se réfère. Il est aisé de mémoriser des classifications diagnostiques, mais l'analyse méthodologique demande à être bien comprise et assimilée.

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Discussion

WILLIAM SARGANT*

I feel very honoured to have been invited to come over to Montreal to attend this Conference. But it was only very recently that I was asked to open the discussion of this first paper, and unfortunately I only received the summary of it ten days before I was due to leave London, and did not get the full copy until I was just on the point of leaving. I have, therefore, had no real opportunity to prepare any detailed analysis or criticism of what, however, seemed to me today, and on reading it, to be a most excellent and balanced paper on what is after all a most difficult subject. It seemed to me to be particularly valuable as a statement of the very unfortunate present position in which we now find ourselves trying to classify and to form concepts about a group of diseases of which we have as yet absolutely no real knowledge as to their fundamental causation, and only some recently discovered empirical treatments with which to help them. Naturally, when so much vital information is lacking, any discussion on classification and concepts is bound to be difficult and mostly speculative. Much of what we are going to say today will become of merely historical interest once we do really start to learn more about the actual causes of the various types of depression met with in everyday practice, how our empirically effective treatments work, and also more about the nature of the constitutional soil on which the various types of depression seem to flourish.

In England all the various theoretical concepts and classifications of states of depression have led to much argument among several generations of psychiatrists. Time and time again in the last fifty years we have seen distinguished psychiatric experts at absolute loggerheads with each other as to whether, for instance, all depressions are manifestations of one and the same underlying disease process, or whether there are quite different aetiologies even of endogenous depressions, or whether or not anxiety states and depressive illnesses are really only two aspects of a long continuous spectrum of the same affective illness. And still the arguments go on and on in the absence of any real knowledge as to their causation.

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Many of the arguments about present classifications and concepts of depression are also surely hangovers of the days I so well remember when I first entered psychiatry, when there were no treatments at all for this group of illnesses apart from psychotherapy, which so rarely worked. But I feel that the whole position should have now changed radically with the emergence of all the new and really effective physical treatments for this group of illnesses. I am one who believes that it is still necessary to distinguish psychogenically induced reactive depressions from the more endogenous types of illness, the former sometimes responding to psychotherapy but the latter very rarely. Once we have done this, most of the endogenous depressions may, in point of fact, be found to form part of one big disease entity with a possibly common aetiology. But now that we have so many different empirical physical treatments (some of which we are going to discuss at this conference) it is becoming more and more necessary, even if there is a common aetiology for most endogenous depressions, to try to subclassify these depressive states so as to prevent ourselves from committing disastrous treatment blunders. Probably, what mainly differentiates the clinical pictures and the treatment responses seen in the various types of endogenous depression are the underlying personality make-up and the body-builds on which the common depressive processes, whatever they are, come into play. For instance, if there is a previous hysterical personality, or an obsessive personality, or a markedly anxious one — or if there is a heavy body build, or asthenic constitution — quite different clinical pictures may present themselves, and quite different treatments may be found necessary. And this is where subclassifications may become so useful and necessary.

Now I think Dr. Lehmann's paper has tried to deal with many of these points, and he is to be congratulated on the way he recognizes and draws attention to all the complicated interrelated patterns that can and do exist in such patients. I notice myself that, in classifying my depressions, I am increasingly starting to do so, not only using the old formulations, but also according to their particular responses to treatments given. Until we learn more about the causation of depressions this may be a very necessary classification stopgap. For instance, before we had learned much about the causation of the anaemias, it was quite useful to classify the various types of anaemia in the way they responded to iron, liver and other blood-forming agents. Now I find myself often classifying true involutional depressions as consisting of those middle-aged patients with obsessive and rigid personalities who respond well to electric shock treatment, and who show the typical diurnal mood swings, early morning waking, indecision and retardation so often seen in this group of patients. When there is present much more anxiety, hypochondriasis, or hysterical features, one tends to subclassify and separate these from the main group of involutional depressions because one knows they will not respond half so well to ECT. Such sub-classifications are probably useful, since once such differences are recognized, there are also different treatments such as modified insulin, leucotomy, iproniazid, chlorpromazine, meprobamate and other treatments which can all be used, together or apart from ECT, in the more satisfactory treatment of such "atypical" involutional depressions. It is the same with the manic depressive syndromes. One must learn to distinguish and subclassify, for treatment purposes, those patients who have periodic attacks and in whom ECT, if given too early in an attack, may only do harm and very little good, and whose past treatment history points to the fact that they only respond to ECT near the expected end of their depressive phase. Then there are other cyclical depressions which we find to be quite unresponsive to ECT in the early stage, but which do respond early and very well to the new drug iproniazid; presumably this will lead to the forming of another subgroup of these recurrent cyclical depressions. Likewise, most classical manic-depressive states, following leucotomy, will show their old typical recurrent mood swings, only the severity of these being minimized by the modified leucotomy operation. There are, however, other recurrent cyclical depressions which we must now try to distinguish and classify as a different subgroup. Following operation, these do not get any further recurrent swings of mood; and these are generally patients in whom exogenous and environmental factors seem to play a larger part in precipitation and perpetuation of recurrent attacks of depression and excitement.

Now I am making these points on treatment in this discussion on the classification and concepts of depression because this conference is going to be, I believe, primarily one on treatment. And I do sincerely hope that in our discussions about treatment at this meeting we will not talk too much about depression in too broad general terms, without also considering all the subgroups that exist, at least in regard to their known and demonstrable treatment responses. I am sure we shall not get very far if speaker after speaker just gets up and talks about so many per cent of all depressions being helped by this or that new drug. Because of the variety of treatment subgroups seen in depressive states, this can be completely misleading, and one's percentages will always depend entirely on the sort of depression that happens to have been chosen for any particular treatment given. If I have one bee in my bonnet at the present time it is about those sometimes foolish psychiatrists who proclaim to the world that because their own percentage of improvement does not carry statistical significance when a drug is tried out on a completely mixed bag of depressions submitted to double-blind sampling tests, this means that the particular drug being tested is worthless. I am reminded of the days when the so-called "quinine doctors" were treating all fevers with quinine because some of them were seeing such really dramatic results in the treatment of tertian ague or malaria. Modern psychiatric statisticians and double-blind samplers, had they been asked to test the value of quinine by modern statistical methods, might well have proved that it was of no value at all in a general group of fevers, and they would thus have completely overlooked its supreme value as a life-saving measure in one subgroup of fevers, namely, malaria. The analogy is most apt. It is only when we have discovered, by patient bedside observation and skilled clinical judgment, how many treatment subgroups exist in depression, and how each seems to respond to a particular drug or treatment, that we can even start to draw any real and valid conclusions from statistics, which should generally be applied to these special subgroups instead of lumping all depressions together as is so often done today. I would, therefore, again like to thank Dr. Lehmann for re-emphasizing all the various types and degrees of clinical depression that do exist, and also for again directing our attention to the

many clinical facets that must always be taken into account, especially before we seek to judge the value or lack of value of any particular treatment in this wide and diverse group of illnesses.

General discussion from the floor (summarized)

In the general discussion which followed, the role of guilt as the core of depression was raised, as well as the question whether guilt was a form of anxiety, and how well one could differentiate between anxiety and depression. There was further debate on the physical or constitutional substrata for depression. It was agreed that the presence of a biological predisposition does not negate the usefulness of psychological treatment, nor does the presence of psychogenic factors deny the value of physical treatments.

The symptoms of depression were broken down into primary ones, viz., disturbances of thought, mood and motility (classical triad), and secondary ones, viz., insomnia, weight loss, hypochondriasis, self-depreciation, etc.

PSYCHOSOMATIC ACCOMPANIMENTS OF LATENT AND MANIFEST DEPRESSIVE AFFECT

R. A. Cleghorn and G. C. Curtis*

Melancholia has been associated from earliest times with somatic symptoms, but only nebulous and fanciful explanations could be given in the absence of either a sound psychology or an established physiology. The 19th century saw tremendous advances in the description of depressions, the emergence of a new psychology, and the development of physiology, while the first half of the 20th century saw the elaboration of psychological proposals that invigorated the intellectual approach (1-4). Recently there has been an increasing interest in depression and other affective states and in their somatic accompaniments (5-10), with some promise that more precise methods of observation and new techniques of modifying the mood (11-13) may lead to clearer conceptualizations and better therapy. This hope is modified by two sober realizations. The first of these is the recognition of the great complexity of affective conditions and the attendant inability to identify with certainty the salient contributing factors and pertinent psychophysiological mechanisms involved in producing a depressive affect. The second is the realization that a patient may be suffering only from somatic symptoms which are believed to be an expression of a psychologically undeclared depression. As Kral (14) has recently pointed out, Bonhoeffer (15) described typical neurasthenic-like depressive reactions in 1912. Kraepelin (16) described dyspeptic symptoms as being indicative of depression. Since then many psychosomatic illnesses, such as ulcerative colitis, have been alleged to be expressions of a depressive reaction, at least in part (8). Of more relevance to our considerations today are those symptoms, such as fatigue or gastrointestinal complaints, which are being assessed more and more commonly as manifestations of depression. They allegedly constitute an expression of depression and have been designated as: anacastic (17), incomplete or clinical (18), promotion (19), masked (14, 20), depressive equivalent (21), depressions in disguise (22). These designations leave something to be desired, either because they are too restricted or too nebulous. The use of a term or a phrase which indicates more about the relationship to underlying processes would be an advantage. Hence, we suggest that somatic symptoms associated with a clinically indisputable picture of depressive reaction be spoken of as symptoms of "manifest depressive affect," while those not so associated but which are believed to represent "masked depression," to use the term preferred by Kral, may be spoken of as symptoms of "latent depressive affect." This, we believe, gives more semantic clarity yet does not commit one to either a meta-psychological or physiological position. In the present state of knowledge such an attitude of tolerant ambiguity is desirable.

There is suggestive support for attributing symptoms to a latent depressive affect in those cases showing relief of symptoms following treatment appropriate to classical depressions. Care must be taken in these circumstances to avoid overlooking the influence of several other factors which bear on the outcome, such as placebo effect, hospital milieu, and the magic of transference. Only when these can be judged to be of minor significance and when less specific measures have failed, can one be reasonably sure that the therapy altered a depressive affect. Even then one is faced with the fact that electroconvulsive therapy, for example, is also effective in certain cases of acute schizophrenia. That, however, opens the converse question as to whether a latent depressive affect is an important component in that state or not.

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Psychosomatic Considerations

The concepts and principles used in an attempt to understand the psychosomatic processes in depression are no different from those used in attempting to understand psychosomatic processes in other disorders. In common-sense thinking and in good clinical practice the unitary approach to the mind-body problem is desirable and fruitful. This means "treating the person as a whole." However, scientific formulations and methods have divided man into mind and body and one must accept the fact that his fate is like that of Humpty Dumpty, of whom it is said:

"All the King's horses and all the King's men
Cannot put Humpty together again."

Hence in this presentation a position of dualism with interaction will be taken, on the grounds that to deny the lack of an acceptable unitary concept does not solve the problem. An attempt will be made, however, to juxtapose those concepts concerning mind and body which seem most relevant to a consideration of their interaction.

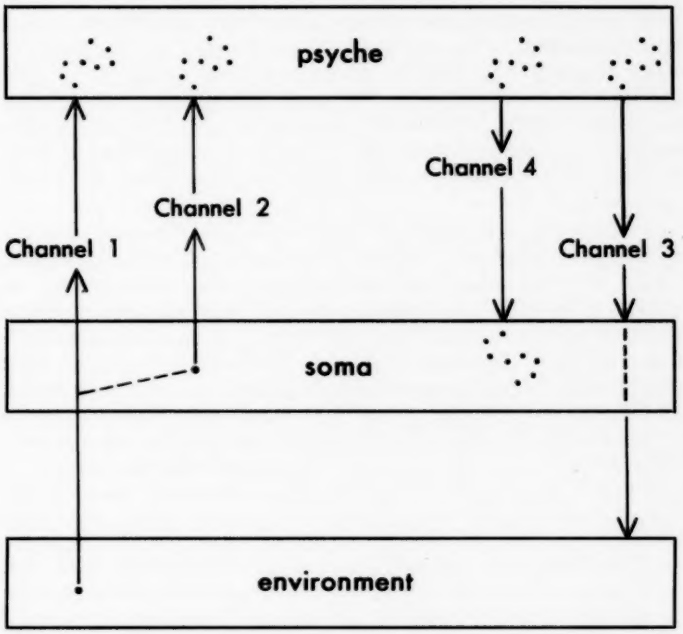
These ideas are presented schematically in the accompanying diagram. The psyche is represented as a "thing" apart from the soma. It is endowed with human characteristics. It has awareness; it sends and receives messages; it ignores; it pays attention; and it interprets. Messages from the environment pass directly through the sensory apparatus (part of the soma) over what we have designated as Channel 1. These messages are not usually distorted greatly except in neurological disorders or hallucinatory psychoses. However, in some manner there is a considerable amount of "tuning in" or "tuning out," and the messages are subject to "correct" or "incorrect" interpretation. The somatic pathway which handles messages to the psyche about the state of the soma is designated as Channel 2. Of course, some of its transmission lines are used in common with Channel 1, and in fact the division is arbitrary. Channel 3 is used by the psyche to send orders to that part of the soma which is at its immediate command, i.e. the striated muscles. Channel 4 is used to send orders to that part of the soma where the psyche has a voice in overall policy matters, but where many of the executive actions and all the details are handled by the soma.

If a patient complains of a somatic symptom or sensation, the doctor can only presume that messages are arriving in the psyche saying that something is happening to the soma. Several possible interpretations exist:

1. *False messages.* This is presumed to be the case when biological methods of investigation can offer no explanation as to why such messages should arise. Such a state of affairs is usually given a label such as hysteria, hypochondriasis, somatic delusion, or somatic hallucination. These conditions can be shown to have meaning when studied by psychological methods, and the messages are presumed to arise in the psyche. Szasz (23) has presented a useful discussion of these conditions under the heading of increased interest in the body on the part of the ego.

2. *Correct messages.* Biological investigation may provide the doctor with a satisfactory explanation as to why such messages should arise, leading him to agree with the patient's psyche. Acute appendicitis is the name given to one of many such conditions. However, other considerations may lead the doctor to conclude that the psyche's orders are wholly or partly responsible for the somatic changes. This is the case with aching muscles accompanying emotional tension, and presumably due to prolonged mechanical tension of antagonistic groups. This is also the case with painful hypermotility of the stomach and duodenum attributed to emotional stress.

3. *Uncertainty or mixed interpretation.* After all the biological and psychological investigations at his disposal, the doctor may still be confused. He may hold the



Channel 1: Somatic sensory system.

Channel 2: Somatic and visceral sensory system.

Channel 3: Innervation and control of voluntary muscle.

Channel 4: Autonomic and humoral systems.

Fig. 1.—Pathways of influence between mind and body.

psyche responsible but not know whether he is dealing with a type 1 disorder, a type 2 disorder, or a combination of both.

4. *Failure of reception.* The psyche may deny receiving any messages when the doctor thinks it should. This is the case with hysterical anaesthesia, hypnotic anaesthesia, painless self-amputations by schizophrenic patients, and failure to perceive minor wounds while intensely preoccupied with something else. Apparently the psyche is not paying attention or has the receiving set turned off.

Hence it is apparent that one can make valuable use of the reported and inferred experiences, sensations, or symptoms of patients, but one cannot use these to draw conclusions about biological processes without corroboration by appropriate biological methods. This warning is not particularly germane to clinical medicine proper, but it is to psychosomatic work. For example, if an emotionally disturbed patient complains of heart palpitations he is often assumed to have tachycardia

even though his pulse rate is not counted. If he has a warm or burning sensation in the stomach, he is often assumed to be secreting excessive gastric hydrochloric acid, even though his gastric juice is not examined. Inferences of this type are undoubtedly correct in a number of instances, but have apparently given rise to many notions in psychiatry which deserve the same status as folklore and old wives' tales.

With the above discussion as a background we propose to present the remainder of our material concerning depressive affect under two broad headings: (1) somatic symptoms and complaints encountered clinically in association with depressive affect, and (2) the apparent relationship between depressive affect and certain biologic processes.

Somatic Symptoms: Muscle and Special Senses

Fatigue: This is perhaps the most common complaint. It is said to be seen in approximately 75% of manic-depressive cases (21) and is obviously disproportionate to effort. It is intense, persistent, unrelieved by sleep, though it may show diurnal fluctuations, improving as the afternoon progresses. It may be focussed on a part and expressed as gross weakness of arms or legs. Attempts to explain fatigue have been disappointing. It is a complicated subject, but in depression it is quite unrelated to decrement in performance, which is more characteristically found in studies of sustained effort (24). As Schwab points out, it is often associated with inadequate performance and poor judgment. There are many instances in which transient fatigue appears as a manifestation of frustration or boredom in otherwise healthy persons. It is dissipated by the solution of difficulties or at the prospect of entertainment. In this it is like other dystonic affects seen in healthy but dissatisfied persons. Whether it represents quantitative or qualitative differences in neurophysiological mechanisms is quite unknown. Cameron (25) feels that they constitute an intensification of activities normally present. Shands and Finesinger (26), in a perceptive but insufficiently appreciated article, describe fatigue as equal in importance to anxiety but opposite in sign, representing a withdrawal of effort.

Aching muscles: These symptoms may be associated with, or independent of fatigue, and felt in the arms, legs or trunk, or as headache. Not infrequently, muscular twitchings are an associated annoyance.

Paresthesias: Complaints of changes in specific sensations are frequently presented as symptoms affecting various systems. The patient utters grievances concerning alterations in skin feelings, from 'funny' or 'bizarre' in nature, to complete numbness. Vaginal or anal pruritus (27) may represent the projection of depressive affect. Visual disturbances, such as fogginess or annoying brightness of lights, may be encountered, despite complete absence of alterations in visual function upon objective examination. Increases in, and distortion of, auditory sensation may be experienced, and change in taste or a burning tongue may be the outstanding focus of pathological inference.

Body image distortions: These constitute a logical extension of the above disturbances which must depend on a central upset in function. The alterations in central nervous system functions are obviously widespread, involving perceptual processes, autonomic centres, and voluntary nervous processes as manifested by changes in posture and synkinetic bodily movement.

The transition from the expression of the above complaints in a neurotic and plaintive fashion to an intransigent hypochondriasis may be inevitable and constitute a transition to the stage of somatic delusions.

Somatic Symptoms: Autonomic Disturbances

Widespread and varied disturbances of the autonomic nervous system frequently accompany depressive affect, either manifest or latent. In the latter case

particularly, patients frequently first seek their general practitioner or surgeon, who may find that the complaints make little diagnostic sense. Kraepelin (16) seems to have been impressed by the autonomic symptomatology, but few since him have accorded it so much attention. Campbell (28), in discussing manic-depressive disease, rectifies this lack, devoting a lucid chapter to this end. He claims that in his series of 522 cases, of which 67.7% were females, the predominance of autonomic over purely psychic manifestations was found in 82% of cases. He lists 29 symptoms that he attributes to the autonomic. These cannot be enumerated and dealt with in detail here, but will be considered under 3 major headings.

Gastro-intestinal: Constipation and gaseous distension have long been associated prominently with depression. The usual inference is that there is inactivity of the parasympathetic nervous system, but over-activity of the sympathetic division, either alone or concurrently, seems probable. Henry (29) described hypotonicity and hypomotility in the retarded depressive, but also found the same in the involutional melancholic, in whom agitation was the marked psychic feature. It should also be remembered, of course, that failure of perception of sensory signals for evacuation may play a part in the genesis of the gastrointestinal symptoms. Other disturbances, such as pylorospasm, diarrhoea, and epigastric distress, are occasionally seen. The pylorospasm may prevent eating (28), and the patient then be assessed as anorexic, though questioning may indicate the presence of hunger. The above symptoms are, of course, not pathognomonic for depression, as they also occur in the neuroses.

Genito-urinary: Frequency of urination is said to be met usually in early and recovery phases of the illness (21). Loss of potency is a very common phenomenon, and the loss of sexual desire becomes more profound as the depression deepens; though erectile potency depends on parasympathetic impulses, the impairment is probably a central rather than a peripheral dysfunction. Menstrual disturbances, such as a delay or change in flow, are more closely related to hypothalamic function mediated through the anterior pituitary (30), though local uterine vascular changes may theoretically be conceded to contribute to alterations in flow. Nymphomania has been described by Campbell (28) as associated with vaginal pruritus, which he assesses as basic to the former drive.

Cardiovascular: Vasomotor changes similar to "hot flushes" experienced with the menopause occur without demonstrable cause in many instances. Vascular spasm may cause extremities to cool so severely as to simulate Raynaud's disease (21), and blotchiness of the neck and face is common, while a generalized rash may appear. The unbearable anal pruritus commented on by Macalpine (27), and the vaginal pruritus, may have their origin or development in dystonic autonomic impulses. Headaches may have a vasomotor origin as well as an origin in somatic muscular tension, but without special attention it may be difficult to differentiate. Tachycardia may be associated with dyspnoea and weakness, corresponding to the neurocirculatory asthenia syndrome, and in certain cases at least may represent a manifestation of depression (28). An elevated blood pressure is also a not uncommon finding, one which subsides with improvement in the situation, as do the other autonomic symptoms.

Somatic Symptoms: Rhythmic Vegetative Functions

Certain rhythmic vegetative functions are notoriously upset in frank depressions. We are accustomed to attribute these to hypothalamic disturbances, though our concepts are quite nebulous as to how this tissue and collaborating systems such as the rhinencephalon and reticular activating systems are involved in depressive conditions. To talk as if we did know may convey a sense of security, but one which is spurious.

Diurnal fluctuation of physiological functions is normally noted by refined technical measurements. In depressions, however, the patient notices gross exaggeration of symptoms in the morning, and often some relief as the day goes on.

Sleep: This indescribable phenomenon exhibits a wide variety of disturbed patterns in disturbances of depressive affect. Insomnia, characterized by difficulty in falling asleep, is common, but early waking may be more characteristic. Hypersomnia may be the contrasting picture, but rarely is such sleep experienced as "restful." Experimental studies (31) and clinical observations in cases of encephalitis (32) indicate centres important to sleep regulation in the vicinity of the hypothalamus.

Feeding is a word which more accurately describes the essential activity leading to food intake than appetite. It may be a less elegant form than the commoner designation, but appetite is a grossly misleading word which denotes an anticipatory attitude or actual relish, but says nothing about quantity of food ingested. A good appetite (relish) has been reported by a lady whose measured intake was 500 calories a day (33). Some individuals have no declared appetite and deny hunger, but eat or feed adequately. Inadequate food intake, described as anorexia, is indeed a prominent symptom of depression, but is probably more an expression of a central than a peripheral phenomenon, despite the work of Henry (29) which describes gastroptosis and decreased secretions in the depressive phase. The opposite behaviour, namely bulimia, seems to represent a vicarious attempt to relieve other tensions. Diurnal fluctuations may be observed during the initial or recovery phase of the illness, with little food being taken in the morning.

Weight loss can be attributed to at least two factors other than inadequate caloric intake. These are the increased energy expenditure with less rest and/or more muscular tension, and an increased secretion by the adrenal cortex of 17-hydroxycorticosteroids (34, 35), which favours protein catabolism.

Menses: The hypothalamic control of the gonadotrophic hormones of the anterior pituitary is probably the cardinal feature in upsets of menstruations which are associated with depression (30).

Relationship between Depressive Affect and Biologic Processes

Currently much thought and interest in psychosomatic medicine is focussed on the subject of depression, largely under the leadership of Engel and his co-workers. This interest arises out of the clinical observation of the frequency with which the onset or exacerbation of recognized somatic disease is preceded by: "(1) some disturbance in a key relationship, real, threatened or fantasied; and (2) an affective state characterized by such terms as helplessness or despair." (5) Data supporting this thesis in regard to ulcerative colitis have been amassed by Engel (5), in regard to lymphomas and leukemias by Greene (36), and in regard to a general medical population by Schmale (37). These workers characterize the affective state as depression. The term as they use it would appear to include most of those states which are termed depression in clinical psychiatry as well as other states which lie beyond the usual clinical concept of depression. On the basis of clinical experience, Engel (5) postulates "that the helplessness consequent to the disturbance in the key object relationship may be regarded as evidence of a traumatic separation process and that such a state may be accompanied by biochemical or physiologic derangements which permit initiation of a variety of pathologic processes in tissues . . . ." It will be noted that this hypothesis shifts the emphasis from clinical syndrome to affect. Engel and his co-workers have not so far attempted to test this hypothesis by collecting biochemical or physiologic data, except in one very important study which will be discussed presently.

Hundreds of biochemical and physiologic investigations by other workers are applicable only in a gross and limited way, partly because of technical limitations and partly because they were for the most part performed for a different purpose. These studies can be divided roughly into those of the early part of the 20th century and those of the 1940's and 1950's. The work of the early 20th century was performed mainly in a search for somatic pathology to account for manic-depressive psychosis as described by Kraepelin. These can be summarized quickly by saying that every accessible cell, tissue and fluid was studied by every technique available at the time, with negative results. Certain manic-depressive depressed patients exhibited a slightly elevated oral glucose tolerance curve which reverted to normal on lifting of the depression. Some were found with mild hyperglycemia and others with mild hypoglycemia. However, in no respect did the glucose metabolism differ significantly from that found in patients suffering from schizophrenia, anxiety, or the all-inclusive "emotional tension."

Modern workers disposed to the clinical syndrome approach have turned their attention mainly to schizophrenia, again with negative or nonspecific results. A summarizing statement by Sands (38) regarding schizophrenia may be instructive in considering the biologic work on manic-depressive psychosis: ". . . the most significant fact emerging from the investigation of schizophrenics is that the range of whatever somatic function one examines is considerably wider than that found in normal control groups."

The application of this notion to the clinical syndrome work on manic-depressive illness would help to explain the contradictions, the opposing findings, and the failure to find anything consistent and definite. It would also lend basis to the practice of shifting emphasis away from the clinical syndrome to other concepts, such as affect, which has been discussed recently in a thorough fashion by Knapp (39).

Modern studies on depression have tended to make this shift, though retaining some interest in clinical descriptive features. Currently they show some promise of a more rewarding comprehensiveness. One such study is that by Engel and Reichsman (6, 7) which has already been alluded to. Their subject was an infant with a gastric fistula on whom they made observations between 15 and 24 months of age. They were particularly concerned with what they termed "depression-withdrawal" and "depression-unpleasure" reactions. In the absence of verbal contact the application of the term depression was based on the empathic response of the majority of observers, on the resemblance of posture and facial expression to that of adults experiencing comparable affects, on the resemblance to Darwin's description of grief, dejection and despair, and on the resemblance to Spitz's description of infants with hospitalism and anaclitic depression (40). As the authors point out, however, there are important problems in establishing the relationship between depressions of infancy and those of adulthood. During the depression-withdrawal reaction of the infant, there was a profound reduction in the secretion of hydrochloric acid and pepsin by the stomach, and histamine failed to stimulate acid secretion. Heart and respiratory rates were either unchanged or slightly slowed. During "depression-unpleasure" there was marked tachycardia, and gastric secretion tended to increase. These reactions were transient and could be provoked and terminated at will by the investigators.

The sedation threshold as described by Shagass (41), used in Montreal as an adjunct for the diagnosis of depressive illness, is not related to depressive affect *per se*. Instead it seems more related to character structure, to anxiety, and to the presence or absence, acuteness or chronicity, of psychosis, though it helps to distinguish psychotic from "neurotic" depressions.

Persky, Gamin, and Grinker (42) found that the rate of urinary hippuric acid excretion after the administration of sodium benzoate was correlated with the level

of free anxiety in the subject. Fabisch and Fellner (43) found hippuric acid excretion decreased in twenty patients with schizophrenia (mainly chronic) and with prominent elements of withdrawal, as well as in depressed patients mainly with reactive or "neurotic" depressions. It will be noted that Shagass's sedation threshold, on the contrary, was elevated in the neurotic depressive group. We are not able to locate hippuric acid data on psychotic depressive patients which might appropriately be compared with Shagass's psychotic depressives.

Board, Persky and Wadeson (34) found significantly elevated levels of plasma 17-hydroxycorticosteroids in depressed patients. The levels were highest in the most retarded patients and in those showing disintegration of defenses. This finding, of course, is not specific for depression.

The biologic findings of these later workers do not bear directly on Engel's hypothesis cited previously. However, they do seem to indicate that greater productivity may result from other more detailed or subtle psychologic observations than from classification of clinical syndromes. Even apart from biologic considerations, there seem to have been observers of human emotions and behaviour in all periods who were impressed with the arbitrariness of classifications. Lewis (4) says: "Manic-depressive psychosis is a provisional group of heterogeneous disorders." We are of this persuasion, which was quite clearly stated by Hoche (44) in his criticism of Kraepelin's classifications, as quoted by Lewis (4):

"It is here that a kind of thought compulsion, a logical and aesthetic necessity, insists that we seek for well-defined, self-contained disease-entities, but here as elsewhere, unfortunately, our subjective need is no proof of the reality of that which we desire, no proof that these pure types do, in point of fact, actually occur . . . That we can predict the patient's behaviour; that, from certain features, in themselves insignificant, we can yet, as a rule, soon obtain a picture of an individual's inner psychic activity; these facts surely depend, not on the existence of disease-types, but on experiences of a much more general nature, which are quite independent of the question of the labelling of these states."

The same problem exists, however, if one turns one's attention to affects or other concepts. As Cameron (25) has demonstrated, patients with anxiety also show depression, and vice versa. One is merely faced with the necessity to form a judgment as to which predominates.

Two aspects of the problem remain to be mentioned — the first pharmacological, the second psychological. The former concerns the depression sometimes accompanying the therapeutic administration of adrenal steroids (45). This bears all the clinical characteristics of a naturally occurring depression. The same agents more frequently elicit the opposite mood state, euphoria, but increased adrenal activity induced by ACTH has been demonstrated not to change the mood in depressed patients when tried experimentally (46). It is of interest to note that cortisone-induced depressions respond to ECT. Rauwolfia or its derivatives and chlorpromazine have been alleged to elicit characteristic depressive states, but this has been questioned by Ayd (47). At the other end of the spectrum of psychobiological perspective is the problem of depression and obesity. This has received most recent attention from Stunkard (48), whose observations establish some important data. It is pertinent to note that considerations in the field of obesity come close to tying together psychological problems of orality and the physiological substratum as represented by hypothalamic mechanisms.

Conclusions

Somatic symptoms accompanying clinical depression may convey only psychological meaning or a combination of biological and psychological meaning. Except

for those symptoms which are obviously hypochondriacal or delusional, one is usually at a loss to pinpoint the interplay of mechanisms which produce a particular symptom in a particular patient. This applies whether the depressive affect be manifest or latent.

There are in existence hypotheses that depressive affect may render human beings more susceptible to somatic disease. Crucial data bearing on this point have yet to appear. The obtaining of such data will probably require recognition of the complexity and intermingling of forces which take place at both psychological and biological levels.

The only purely biological events known to precipitate depressive reactions which are indistinguishable from the naturally occurring ones are the administration of cortisone-like adrenal steroids, or ACTH, in grossly unphysiologic quantities, or possibly certain ataractic drugs. Neither event regularly produces such a reaction, and the necessary and sufficient conditions for the occurrence of the reaction have not been defined.

Résumé

Les réactions affectives que le psychiatre qualifie de dépressions, sont presque invariablement accompagnées de plaintes se rapportant à un trouble physique ou présumé tel. Ce fait est si banal qu'il ne suscite ni intérêt, ni commentaire, bien que la plupart des psychiatres aient tendance à mettre ces symptômes sur le compte de l'activité du système nerveux central, en association avec le désordre affectif.

Ces dernières années, on a mis nombre de doléances de nature somatique sur le compte d'une dépression, c'est-à-dire d'une maladie qui ne se manifeste pas clairement par les signes psychologiques habituels. Pour éviter l'inconvénient des dénominations variées qui ont été appliquées à des situations semblables, les auteurs proposent de désigner tout symptôme somatique associé à une dépression mal caractérisée ou masquée, par les termes "causé par" ou "avec dépression latente". Les mêmes symptômes physiques peuvent être associés à une "dépression manifeste" ou classique.

Dans cet exposé, les auteurs passent en revue un grand nombre de plaintes de nature physique, exprimées au cours de dépressions latentes ou déclarées, et tentent de saisir leur signification et leurs mécanismes. Ils décrivent également des changements dans les fonctions physiologiques et discutent les hypothèses relatives aux mécanismes centraux qu'ils impliquent.

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Discussion

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I should like to thank Dr. Cleghorn and Dr. Curtis for their instructive paper. Even if the somatic complaints, or the somatic equivalents which I personally prefer, in the manic-depressive psychosis are well described since Kraepelin's time, and even if these symptoms especially following Campbell's work have had a more prominent position in the discussion of this disease, it is still very useful, not least from a diagnostic point of view, to emphasize the occurrence of these phenomena.

As you perhaps will know, the manic-depressive psychosis plays a crucial role in the psychiatry of the Scandinavian countries, and especially in my country, in Denmark. It is perhaps the most frequent and important of the major psychoses, the frequency being about 2% of the general population. So we are very eager to acquire information on other psychiatrists' viewpoints concerning the symptomatology of the disease.

It is not an easy task to open discussion on the paper we have just heard, since the paper is very concrete and explicit in its statements. But I should like first of all to say a few words about the phenomenology.

The conceptual boundaries between the psychic and somatic symptoms are often difficult to draw. Let us take the phenomenon of fatigue. Of course, fatigue is a very common complaint in depressed patients. But often it appears that what the patient talks about when he indicates he is tired is the lack of vital tone or vital feeling, which again is without sharp boundaries and appears to be identical with phenomena of feelings of self-insufficiency, of self-depreciation, of guilt feeling, of self-accusation. It is true that in many cases you will find complaints of fatigue such as Dr. Cleghorn calls "symptoms of a latent depressive affect." But often this tiredness will be of another character, have another flavour than the fatigue which appears following a severe somatic disease such as influenza or pneumonia. It does not have the character of physical exhaustion, but is characterized by a lack of impulses to act, a lack of spontaneity, by a tendency to be overwhelmed by small problems. That is what a patient calls fatigue. But evidently it is quite another thing than physical or somatic tiredness.

Another symptom about which I do not think we have heard very much, and which also must be placed between psychic and physical symptoms, is sleep disturbances. These, I guess, are the most frequent symptoms of a latent depressive affect, and of course they have to be taken into account when we are talking about fatigue in these patients.

Now a few semantic remarks: Dr. Cleghorn and Dr. Curtis are most cautious in proposing the terms "symptoms of manifest or latent depressive affect," claiming that this gives more semantic clarity, yet does not commit them to either a meta-psychological or physiological position. Nevertheless they give their paper the title "Psychosomatic Accompaniments of Latent and Manifest Depressive Affect." Of course, the term psychosomatic is logically correct as far as we have here to do with the patients' statements as to their subjective experience — so far as it is a psychological phenomenon. But I think we

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are all thinking about something more concrete and explicit using the term psychosomatic: namely, used in this connection, that the patients' somatic complaints should be secondary in relation to a latent or manifest emotional disturbance — and this from my point of view is not a neutral statement.

Personally, I think that the depressive affects and the somatic peripherally located phenomena are in some cases determined by the same biological disturbance in the mid-brain — here first of all the dominating autonomic disturbances; while in other cases these phenomena are an expression of a basic emotional disturbance.

When I claim that complaints, especially from the autonomic system, are not secondary to emotional disturbances, are quite independent of them but go parallel with them, it is because very often in the *same* patient one will see in some episodes or phases depressive affect plus autonomic complaints; in others the same autonomic complaints but now without any manifest depressive affect.

In some patients each new depressive or melancholic episode is initiated by a long autonomic phase of a similar character each time. Thus I have a patient in whom each melancholic episode is initiated by heavy vomiting for two to three weeks — and in this period the patient does not feel depressed at all, but is active and optimistic.

It is also worth noting that quite the same autonomic complaints or disturbances are often seen accompanying manic phases in a manic-depressive psychosis. Further, one can see patients with recurring manic phases without any depressive states, and also here one can find autonomic periods without any elevation of the mood.

Following Dr. Cleghorn, one should here speak about "symptoms of latent manic affects," but I personally find it more adequate and reasonable to use the old term *somatic equivalents* in a manic-depressive psychosis.

General discussion from the floor (summarized)

Other discussants pointed out that the kind of inhibition that leads to fatigue and retardation seems to follow a period of sleep and improve later on during the day. Thus, for instance, if such a patient went to sleep in the afternoon, this period of sleep would be followed again by inhibition and psychomotor retardation. The question was raised as to what was the relationship between sleep, inhibition and retardation.

Further discussion dealing with cases in which somatic symptoms were reflected as depressive equivalents raised the following problems: Was there still a depression extant and, if so, where? Should one accept the concept of "unconscious depression" and "latent affect" in depression?

PSYCHODYNAMICS AND PSYCHOTHERAPY OF DEPRESSIONS

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In psychiatric textbooks depressions are classified in different ways. Generally speaking, a differentiation is made between depressions supposedly occurring endogenously and depressions considered reactive where an overwhelming environmental situation provokes the depressive state. In addition to this basic differentiation, depressions are also diagnosed as belonging to manic depressive psychosis, as involutional depressions, as schizophrenic depressive states, and as depressions occurring in the various organic psychoses. The question arises—are all of these different depressions the same clinically, do they have the same psychodynamics, and do they respond in the same way to therapy? In other words, are we dealing here with something uniform even though it occurs in different configurations or settings, or are we dealing with different disorders where only certain symptoms or syndromes are in common? Not knowing the etiology of most mental disorders where the depressive manifestations may occur, today this question cannot be fruitfully discussed. We may say that, clinically speaking, these different depressions occurring in different settings have elements in common, but of course the depressive symptoms are altered, modified and influenced by symptoms of other disorders when they occur in conjunction If we confine ourselves in this discussion essentially to the manic depressive depressed patient and to the so-called neurotic depressions, we see that the clinical symptomatology and the psychodynamics are very similar. This was already apparent to Freud, who began the elaboration of the psychodynamics of depressions with the analysis of the "mourning phenomena." Quoting Freud, Fenichel claimed that if a child loses an object, the libidinal strivings no longer bound to the object flood the child and may create panic. In "grief" the adult has learned to control this flood by retarding the necessary process of loosening the tie to the lost object. This lost object is represented by hundreds of separate memories, and for each of these memories the dissolution of the tie is carried through separately over a period of time. Freud designated this process as "the work of mourning." The mourner has the illusion that the lost person still lives and there is close identification with him. Every mourner builds up a kind of substitute object within himself. Freud pointed out that the universality of introjection as a reaction to the loss of an object applies to all mourners and also to persons in a state of depression. Freud assumed that mourning becomes more complicated, and sometimes even pathological, if the relationship of the mourner to the lost object was very ambivalent. In this case the introjection acquires a sadistic significance. The incorporation then not only represents an attempt to perceive the loved object but also an attempt to destroy the hated object. It can be stated that depression is a complete or partial loss of self esteem. The depressed person tries to undo the loss and actually aggravates it by a pathognomonic introjection of the ambivalently loved object. The depressed person complains that he is worthless and behaves as if he has lost his ego. This turning against the ego was noted by Freud in analyzing the self-reproaches of depressed patients. The self-reproaches were originally reproaches against the object. The depressed patient says, "I am bad because I am a liar," when he wants to say, "I am angry with 'X' because he has lied to me." Freud explains the self-reproaches as accusations directed against the introjected object. Abraham had a similar point of view, and Fenichel states that in melancholia it appears as if the main emphasis of the personality has been shifted from the ego to the super ego. The patient's conscience represents his total

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personality. The ego altered by the introjection is the mere object of his conscience and is entirely subdued by it. Fenichel stresses the role of the super ego in depressions. It represents a protective and punitive power. Under normal circumstances the first aspect prevails. In depressions, regression has abolished the first aspect of the super ego. The whole depressive process appears as an attempt of reparation to restore the self-esteem that has been damaged. In depressions, the ego is helpless and yielding to the attacks of the super ego. The self-reproaches are an attempt to attack the introjected object, but in addition they also represent a plea for forgiveness intended to convince the super ego how much the accusations have been taken to heart.

Freud differentiated between neurotic and psychotic depressions and based the differentiation on the depth of narcissistic regression. To the findings of Freud, Abraham added a few fundamental observations: namely, he found the pregenital foundation of the ambivalence and stated that the patient was as ambivalent toward himself as he was toward objects. He believed this observation was very important because it could also be demonstrated in the interval between depressions when the person very often shows a marked ambivalence about his performance, exaggerating it or minimizing it. The oral sadistic manifestations to which Abraham also called attention are present in interval periods between depressions. Rado clarified the connections between depression and self-esteem. He also believed that the manic depressive periodicity can be explained on a basis of transgression and expiation.

Of course, we would not like to discuss the whole literature on the psychodynamics of depression. Basically, in our opinion, since the work of Freud, Abraham and Rado not a great deal has been added to illuminate the problem further. Fairly recently Ebaugh summarized the psychodynamics of depression and enumerated the main dynamic factors. He mentioned the complete dependence on the mother figure for all satisfactions in life and at the same time the hostile reactions toward the mother, with intervening counter-hostility or rejection by the mother, the suppression of overt hostility, and ingratiation as a crystallization of this hostility. Increased maturity brings acceptance of conscience and external values as well as future hostile impulses which cause guilty conscience and self-blame. He feels that adults are exposed to frustration of need by others or by their own limitations. The suppressed hostility turned against self results in a feeling of guilt which in turn reduces self-esteem. This reawakens infantile survival panic about losing love. Energy has to be withdrawn from the environment to handle these many conflicts. Less available energy for handling real problems leads to a further frustration and a psychic reduction of self-esteem.

The psychotherapy of depression is a complex problem. At present we can distinguish among three psychotherapeutic aspects. First, the psychotherapy of a depressed patient where the main treatment is an organic one centering on shock treatment; second, the psychotherapy of depression which is directed toward eliminating the depressive attack; third, the psychotherapy or psychoanalytic treatment of individuals with depressions to eliminate their depression and to change the matrix of the depression to such a degree that no new attack occurs.

The psychotherapy of depression done in conjunction with organic therapy is essentially a supportive one. This therapeutic function should not be underestimated because it has great value as a palliative treatment even though the main therapy is applied by other means. The ego support that the depressive patient craves and the reassurance which is demanded concerning his fate and preoccupation need a constant and repetitious effort on the part of the therapist. If a patient receives electroshock treatment, the supportive therapy is especially important

for a week or so until the electroshock treatment begins to ameliorate the patient's depression.

Another very important factor is the presence or absence of suicidal danger, which always has to be taken into consideration if psychotherapy is attempted for a longer period.

The psychotherapeutic treatment of a depressed patient is a difficult task for several reasons. First, the difficulty of contact; second, the ambivalence which is present toward the therapist; third, the suicidal danger; fourth, the great demands made on the therapist by the patient, which are most difficult to fulfill if the patient is not in a hospital environment. Such demands are also made in connection with relatives where the patient would like them to behave differently toward him and would like to use the therapist to achieve this end. If this is not forthcoming, or not to the degree which the patient accepts, the hostility of the patient is very intense toward the therapist. We feel that in therapy the most important factor is contact; and we feel that if a patient is severely distressed, he will not benefit too much from psychotherapy, and simply will mark time while receiving reassurance. If the patient is able to partake, his therapy will not be much different from the treatment of other patients, with probably two exceptions. First, the ambivalent structure of the patient has to be discussed again and again and his depression interpreted. Interpretation of the ambivalence and especially the overt or subtle forcing of the patient to make a decision, if not done skillfully, could have negative effects on the treatment. We are sure there is no general prescription how to treat ambivalence. This not only depends on the structure of the ambivalence but also on the general personality functioning of the patient being treated. We found ambivalence one of the most difficult issues in the treatment of these patients and this is also one of the areas where the patient's resistance can be very successfully organized and can stymie psychotherapeutic progress for a long time. Second, aggression in these patients is equally difficult to handle. We found that if patients respond to treatment in the above-mentioned realm, the super ego is much ameliorated.

In mild depressions where the patient is accessible, reassurance of his worth and opportunity to verbalize his anger and disappointment are often therapeutically effective. In more severe illnesses the same approach may have a reverse effect, being misinterpreted by the patient as a demand which he cannot meet.

If we review the pertinent literature we find that we do not have a "psychodynamics" of depression because most of the dynamics are organized around symptoms such as guilt, self-accusatory ideas, self-punishment and self-debasement. The question then arises in how many depressions are the above-mentioned symptoms present. We see quite a number of depressions where self-blame and guilt are not present, especially in the beginning of a depression. Feeling blue and preoccupation with inability or reduced ability to perform prevails. After a while the patient begins secondary elaborations to explain the depression. These explanations are either exaggerations of true happenings or rationalizations. The depressive mood is explained by the inability to perform (actually the alteration of the mood comes first and the inability to work second). The depressed person may then assume that he is physically sick and the symptoms are a direct consequence of his physical disability; this assumption can then ramify into many hypochondriacal explanations. He is usually not supported in such assumptions. It is pointed out to him that he has no physical findings and that the depression has a psychological background. Alternatively, the patient may feel that if he could pull himself together he would be able to function. He is directly or obliquely supported in this assumption by his family or others. He feels that he is responsible for his condition and that

he is no good because he has no equipment to cope with life situations; then appear many of these symptoms of self-blame which are so well known.

The dynamics, as known today, explain these secondary manifestations of the depression but we do not have yet an acceptable dynamic formulation of the depressive mood itself. Rado is aware of this problem when he assumes that the person predisposed to depressions has a special hedonic organization of his own. The depression is obviously a resultant of assumed value. It is of interest that the available dynamics only explain the depression during or after the attack, but are not able to predict the occurrence or recurrence of the depression even in persons whose psychic structure is well known and whose ego organization has been competently investigated. We are struck by observations that many depressions develop during psychotherapy or psychoanalysis which was undertaken to relieve other symptoms. The therapist was unable to foretell the depressive attack; the dynamics, of course, become clear when the person actually becomes depressed. All this indicates the incompleteness of our psychodynamic formulations. We are equally puzzled by the fact that the personality organization is described as responsible for the sickness of patients who, for instance, suffer from involutional depressions. It is generally accepted that such depressions usually develop in persons who are rigid, obsessive, serious, anxious, worrisome. However, why only a certain number of such patients showing this personality organization develop a depression and others do not is not clear. We have a large number of individuals who show a personality make-up which should lead to a depression, but who never develop depression even under serious environmental pressure situations. Therefore, this personality organization only explains the background of the depression but not the depression itself.

Another issue still unclear is the degree or intensity of depressions and their duration. Even if we make the assumption that we are able, at least up to a point, to explain the quality of a depression in psychoanalytic terms, we do not know what factor or factors regulate its intensity. Different patients show different intensities of depressions from superficial to very deep. Sometimes the same person has a mild depressive attack and at other times a severe one. Sometimes the attack lasts a week and at other times many months. Many explanations have been offered to explain this, based on the ego and super ego structure of a given patient, but we do not feel that this important facet of depressive illness is explicable today in any of the available psychodynamic terms. Systematic research in this field, namely the prognostication of the severity and duration of depressions, would probably illuminate unclear and unsuspected dynamic factors. We feel that the relationships of depression to anxiety and aggression will be fruitful avenues of approach, especially if instruments of quantitation can be evolved in this connection.

To what extent a patient who has received electroshock and recovered should receive psychotherapy afterwards is still an open issue. Many psychiatrists express the opinion that such psychotherapy is essential. Unfortunately there is little factual substantiation in the literature. There are practically no studies available that prove the necessity of psychotherapy by comparing the results in patients who have received psychotherapy in addition to shock therapy and those who have not. We believe that generalizations cannot be made and that each case must be appraised individually. There will be patients in whom psychotherapy is essential after successful shock treatment, whereas in others this will not be necessary. There are depressed patients who after the elimination of the depression remain anxious, show quite a number of conflictual difficulties and are not up to par in functioning freely in their environment. It is obvious that such patients would benefit greatly from psychotherapy.

The increased use of different drugs will necessitate new psychotherapeutic techniques. We are sure that regardless of how many effective drugs we have in

the future to treat depressions, many of these patients will always need some psychotherapeutic attention. It is possible that the efficacy of these drugs will decrease the supportive role of psychotherapy; then the therapeutic attempts could concentrate more on problems of personality organization and conflicts, in order to support the patient's adaptation to environmental situations which have significance in provoking or precipitating depression. New techniques have not been reported because the drug treatment of depressions is relatively new. Research is needed very much in this field.

Many psychiatrists feel that it is very difficult to approach a patient in a state of depression because of the obvious difficulties in establishing contact and because of the very ambivalent transference situation developing in many patients. They feel it is better practice to concentrate more on the patient after the depression in order to prevent its recurrence. It is possible to treat a depressed patient with psychotherapy alone without any electroshock therapy and drug adjuncts. The possibility of such a treatment depends upon a number of factors. The degree of the depression is one of the most important. If the depression is not very profound, so that the patient is able to partake of psychotherapy, it can be attempted. Our observation is that anxious depressive patients are more likely to participate in psychotherapy than those who are retarded. In retarded depressions, where the patient is in a state of continuous rumination, such therapy is nearly impossible and very quickly reduces itself to purely supportive measures.

In the psychotherapy of depressions it is important to note in what kind of setting the depression occurs. For instance, a depression with a schizophrenic background is much more resistant to psychotherapy than the ordinary depression. This also applies to depressions occurring in the pseudoneurotic form of schizophrenia and in arteriosclerotic settings. In addition there are certain individual configurations which may determine whether or not the patient will respond to treatment. It is generally assumed that endogenous depressions are more difficult to treat psychotherapeutically than those in which external precipitating factors are in the foreground. However, in some cases it is very difficult to decide how much of the depression is endogenous and how much is not. At times we have seen patients who responded to psychotherapy during the first attack but who failed to respond when the same or similar precipitating factors were present the second time. In all psychotherapeutic attempts to treat depressions the question arises, do we accomplish more than a palliative amelioration of this disorder? If the treatment of a depressed patient with psychotherapy is prolonged it is very difficult to judge whether or not the patient recovered because of the psychotherapy or because the depressive cycle terminated spontaneously. We have seen quite a number of patients in whom psychotherapy was successful at the end of the cycle and was unsuccessful at the beginning of another. Careful statistics on this issue are needed to eliminate the confusion existing in the minds of many psychiatrists. Incidentally, this confusion is transmitted in consultation to the patients, who are not very appreciative of the fact that after several months of psychotherapy they will have to be exposed to shock treatment. We are not very impressed with the value of psychotherapy in the severe endogenous depressions as a sole treatment method. We believe it is very successful in some reactive depressions and also think that persons with anxious depressions, where in addition to the depression many schizoid factors exist, benefit from psychotherapy because they are a group which does not respond well to electroshock therapy.

Some of these patients have a long history of phobic, obsessive-compulsive and other neurotic manifestations. Quite often these patients also show marked schizoid traits. They do not respond well to electroshock therapy, but better to drugs (amphetamine, iproniazid, etc.). These patients benefit from psychotherapy

because it allays their anxiety. This is the group of patients in whom we expect a great deal in the future from a combined drug and psychotherapeutic procedure.

Another issue which has to be investigated much further is to what extent successful psychotherapy prevents the recurrence of new attacks. The organic treatments in depression are not able to do so. It is obvious that patients successfully treated with psychotherapy are not seen again. However, we do see the unsuccessfully treated patients. The number of patients who show a recurrence of a depressive attack after supposedly successful psychotherapeutic or psychoanalytic treatment must be noted, even though it also has to be acknowledged that not too many patients have been treated with psychotherapy alone and therefore statistical conclusions may not be fully valid.

It will have to be clarified further whether depression is a basic manifestation and an indicator of a disturbed emotional homeostasis such as anxiety or aggression, whether it is due to an organic agent, or whether it is due to a failure to cope with serious ego threats. It has also not been determined whether depression is not a defense against anxiety and/or aggression. In the latter case, it would be a secondary mechanism and not a primary one. Any successful theory of psychotherapy in depression should be based on a better etiological understanding of the process than we have available today.

Résumé

On pose le diagnostic de dépression chez des patients très différents. Une distinction est faite en général entre les dépressions qui apparaissent dans le cadre d'un désordre mental, tel qu'une psychose organique ou une schizophrénie, et celles qui naissent (pour ainsi dire) d'une manière indépendante. L'auteur discute la nosologie de ces différentes dépressions, ainsi que leur plus ou moins grande similitude. Les dépressions "indépendantes" sont elles-mêmes divisées de plusieurs manières; le diagnostic des formes maniaco-dépressives, involutives et psychoréactives se base en général sur des caractères cliniques différents. Quelques classifications vont encore plus loin et englobent les formes névrotiques et "psychogènes".

La question se pose à savoir si ces affections sont toutes différentes du point de vue psychodynamique, ou si elles suivent le même schéma. On peut en outre se demander si elles répondent de manière différente à des thérapeutiques variées. A l'heure actuelle, nous ne savons pas encore de façon certaine si des mécanismes psychodynamiques différents peuvent être mis en évidence dans les diverses sortes de dépressions.

La structure d'une forme réactive et sa configuration psychodynamique sont très semblables à celles d'une forme maniaco-dépressive, si l'on ignore le rôle joué par des facteurs "précipitants". Certaines modifications de la psychodynamique apparaissent à une période avancée de la vie, mais elles sont attribuables davantage à l'âge du sujet qu'à des différences intrinsèques dans le schéma dépressif. Il n'a pas été possible d'examiner à fond la psychodynamique d'un patient prédisposé aux dépressions. La plupart des études dont nous disposons n'expliquent la dépression que pendant la crise ou après celle-ci, mais ne sont pas capables d'en prédire l'apparition ou la non-apparition, et cela même chez des individus dont le fonctionnement psychique est bien connu et dont la structure du moi a été disséquée intégralement. Il y a lieu de citer ici les cas de dépression apparus au cours de séances de psychanalyse ou de psychothérapie, et dont le médecin n'était pas en mesure de prévoir l'intrusion. Nous savons que certaines personnes peu sociables, au caractère rigide, anxieux, obsédé, sérieux et bourrelé de soucis, sont victimes de dépressions, en particulier à l'âge des involutions. La question se pose cependant toujours à savoir pourquoi certains de ces sujets sont atteints, et pas d'autres. La

présence ou l'absence d'un facteur "précipitant" ne suffit pas à expliquer l'apparition ou la non-apparition de la dépression, attendu que nous avons trouvé de tels facteurs — et de très sérieux — chez des individus appartenant au type cité ci-dessus, et qui ne réagirent pas par le truchement de la dépression. Par conséquent, les faits qui déterminent l'apparition de cette affection chez un certain type de personnes demeurent inexpliqués.

L'auteur décrit encore quelques-unes des méthodes de recherche susceptibles de jeter quelque lumière sur les processus dépressifs. Actuellement, le traitement de ces cas est orienté vers la psychothérapie, les moyens médicamenteux et l'électrochoc, ou vers une combinaison des trois procédés. Les indications et l'efficacité de ces traitements sont également discutées.

Discussion

ALDWYN STOKES*

Dr. Hoch in the first instance concerned himself with the diagnostic and nosological problems associated with the overall manifestations of depressions. He did so in order to distinguish, from a psychodynamic point of view, a core process regarded as primary for essential depressive illnesses, and secondary unspecific processes which determine depression as a symptom. Since my framework of approach is very different from the psychoanalytic approach, I cannot comment from direct experience on the core process; but from the study of depressed patients in face-to-face interview situations I would agree that the dynamic factors are various in the majority of instances and are akin to those cases where anxiety is the main symptomatic feature.

The relationship of depression to anxiety is, in my view, best conceived by reference to a feeling tone system structurally and functionally embedded in the multiple organ system of the brain. All such organ systems, for example the anti-gravitational system, have developed evolutionally in hierarchical fashion. Therefore it is worthwhile considering the hierarchical development of the feeling tone system. Provisionally a case should be made out for levels of "hurt" function: the lowest would be pain and fear, then anxiety, and lastly at the highest level, depression. The differences in the psycho-physiological manifestation of these "hurt" states would be understandable in terms of different engagements with the autonomic and somatic functional processes at the differing levels of evolutionary development.

Depression is almost exclusively a human affect and might be related to the singular human propensity of forming groups and societies. Nothing has yet been said of the dynamics of the psychosocial process although by implication the psychoanalytic notion of a core incorporation of authority figures opens up the whole psychosocial area. Much has been made of the archaic super ego, its castigation function inappropriately out of phase for liberal adult adjustment; little has been said of an obsolete ego ideal inappropriate to the adjustment problems of those older patients who have entered on the declination period of their life span. Yet in a Western middle class society this failure to live up to self-expectancy is more associated in the older age groups with humiliation and "loss of face" than with conscience. The problem of maladjusted social submergence is, I think, as important as the problem of maladjusted social emergence. Certainly depressive illnesses, common as they are, have a considerable concentration in the older age groups.

Outlived obsolete self-expectancy might well be the key, in some instances, to the prediction of the depressive attack. Dr. Hoch has said that the dynamic processes operative before an attack oftentimes do not allow the foretelling of the illness. The social cues which trigger loss of self-respect and social prestige are worthwhile examining in this regard. In the case of the very important person, or in those areas where we all think of ourselves as very important persons, outmoded self-expectancies are certainly operative and have to be reckoned with in psychotherapy.

Dr. Hoch has stressed in psychotherapy the features of ambivalence and hostility towards the therapist, with the technical difficulties that ensue. From my differing standpoint the same difficulties arise but in different degree. So long as the process of psychotherapy is not too defined in terms of rigidly held technique, great help can be accorded the patient suffering a depression. In this work we become practitioners rather than theoreticians and may use from moment to moment methods selected from many at hand. Such methods *now* include importantly the judicious use of psychopharmaceuticals; *later*, perhaps, a matching of chemical agent to psychodynamic process will be possible.

Dr. Hoch commands our thanks for a most stimulating paper which, in an eclectic group of the sort assembled here, will bring about a surge of new thinking on problems that await solution.

General discussion from the floor (summarized)

It was agreed by many that psychotherapy played an important role in the overall management of many types of depression. There was disagreement on what kind of psychotherapy and for how long. Most participants were able to delineate some types of depression that to date did not seem to respond to any kind of treatment by itself or in combination with other treatments. Special reference was made to the so-called "chronic depression."

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There was an animated discussion of the "toxic" effects of psychotherapy in certain depressions and emphasis was placed on the hazards of suicide in the non-hospitalized depression treated with psychotherapy, no matter how skilled the psychotherapist or how frequently the patient was seen.

The natural history and development of depression from its earliest beginnings was raised under the query — do children manifest depressive affect? Infants and children have been reported in an increasing literature to manifest a host of feeding and toilet training problems, as well as sleep disturbances; the effects of hospitalism and deprivation of continuous mothering have been described by various writers; homesickness and loneliness with and without psychosomatic accompaniments have been noted; children who manifest gross anxiety about separating from parents and refuse to go to school were compared to adult depressed persons unable to go to work because of feelings of fatigue and anxiety. It was pointed out that such children had to be followed until adulthood to observe the outcome, and that a major research task was to study the depressed adults more carefully in relation to their childhood personality organization.

THE PHENOMENOLOGY OF DEPRESSIVE STATES

MARTIN ROTH*

I think it would be generally agreed that the classification of psychiatric illness at the present time is in a relatively undifferentiated and primitive state. It is a noteworthy fact that since the introduction of the Kraepelinian classification of mental illness about half a century ago, not a single new entity has been defined that commands general acceptance. Freud, the most original thinker to work in our field during the last century, left the classification of mental illness as he found it. It may be thought that psychopathological mechanisms such as those he brought into the daylight transcend classificatory systems, creating laws and consistencies of their own that draw their logic and validity from those more fundamental attributes of the mind in terms of which they are formulated. However, having regard to the progress of psychiatry during the past few decades, perhaps even the most devoted and orthodox of Freud's followers would hesitate before making such a claim.

The truth of the matter is that even the hope of discovering a consistent and meaningful psychopathology is largely dependent upon the existence of phenomenological entities that are relatively uniform. It is only then that conditions become favourable for differentiating threads of continuity in life development and in psychological interaction from the infinite complexities of the causal nexus in which they are interwoven.

When Freud began his investigations on psychiatric problems he had achieved considerable success as an investigator in a field of medicine where classification had been advanced by the efforts of such men as Charcot and Marie. When a discipline has reached this level of development, the situation is favourable for the definition of patterns of association that have general validity and possible causal significance. However, psychiatry was far removed from this stage in its evolution six or seven decades ago, and the nosological entities with which Freud set to work were relatively crude and ill-defined. Even Kraepelin's work was only a beginning of systematization.

I have chosen to interpret "phenomenology" as referring to "that division of any science which describes and classifies its phenomena," rather than in the more limited sense in which it was employed by Jaspers and those who followed him in attempting to render the inner life of the depressed individual. For it seems to me that the chances of discovering effective drugs or other treatments for mental illness are limited by our inability to define categories that are relatively homogeneous with respect to their broad characteristics rather than by our ignorance of the unique nuances of subjective experience.

It is convenient to start our consideration of the phenomenological aspects of depressive states with the depressive form of manic-depressive psychosis, partly because our knowledge about this clinical entity first defined by Kraepelin is probably more precise, detailed and reliable than that about any other clinical group. Moreover, the more important practical and theoretical questions which confront us in relation to depressive states in general may be posed in the form of questions about the clinical boundaries of this phenomenon. Thus:

(*a*) Are endogenous and reactive depressions distinct entities, or is one merely a quantitatively more severe version of the other, merging insensibly with it?

(*b*) What are the boundaries of clinical phenomena dominated by depressive symptoms? Is there a single family of affective disorders, or are the anxiety neu-

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roses, for example, deserving of separate nosological status for practical or theoretical reasons or both?

(*c*) Is there such a thing as a depressive syndrome peculiar to one or another part of the life-span, the involutional period or old age, and are the differences implied in some descriptions of a genetic, metabolic or a purely incidental kind?

(*d*) If we deal with a specific predisposition confined to a small percentage of the population, as much of the genetic evidence suggests, what is the significance of the depressive states which are associated with organic disease of the brain? Have they any kinship with endogenous or any other form of depression, and can they teach us anything about the final cerebral pathways utilized by the functional or neurotic forms of depressive illness? Related problems are those associated with the depressive states of alcoholics, epileptics, and with the florid, richly-embroidered depressive states found in association with clouded consciousness.

(*e*) We may ask questions about the overlap between depressive reactions and a number of clinical phenomena with which they have some ill-defined and obscure kinship, such as depersonalization, hypochondriasis, and obsessional states, as also about the underlying personalities, which are so often described as a fertile breeding-ground of depressive reactions.

(*f*) Finally, it is necessary to consider the relationship between states of impaired awareness and affective symptoms, a question that has arisen sharply in recent years owing to the affective changes produced by hallucinogens and also associated with lesions of the temporal lobes. The association is also found in the so-called "mixed" psychoses such as the oneiroid and schizophreniform states and in the acute, affective disturbances occurring in epileptics and in the course of alcoholic intoxication.

These are old and, some would say, old-fashioned problems of clinical psychiatry; many may remember vividly the vigorous discussions around some of them which filled the psychiatric literature 25-30 years ago. Although some advances have been registered since then, it is sad to think that we are not yet in a position to give clear and conclusive answers to most of these questions. This is due less, I believe, to the inherent difficulties of the problems involved than to the fact that only a handful of investigators have availed themselves of the various opportunities afforded by their clinical experience for making observations designed to settle these questions. Progress in relation to these bread-and-butter questions of such great importance for the advance of psychiatry along other fronts is slow, partly at any rate because they lack the glamour that attaches to laboratory work or psychodynamic exploration and have attracted few investigators.

Some Epidemiological Data

If one of the principal purposes of defining clinical syndromes is identification of the causes of disease, the description should always include the facts relating to the pattern of incidence, for such epidemiological data are rightly playing a role of increasing importance in modern psychiatry in defining the limits for investigation, and are sometimes rich with suggestions as to where the aetiological factors may be sought. It will be seen that manic-depressive psychosis is, as far as admissions to mental hospitals in the United Kingdom are concerned, a disease far more common in women than men, the highest frequency of first admissions occurring towards the threshold of old age. Schizophrenia, it will be seen, is in contrast mainly a disease of young men, incidence among males being overtaken by that among women only in middle age (Figure 1).

The first admission rates in Figure 1 probably underestimate the incidence of affective psychosis among old people for reasons that will become clear. A consec-

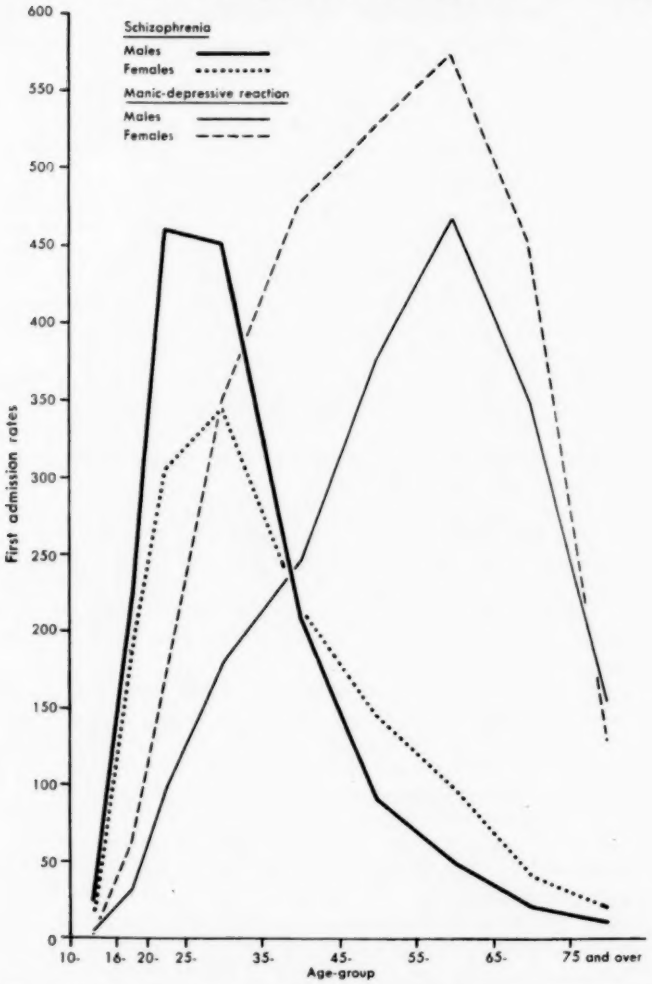
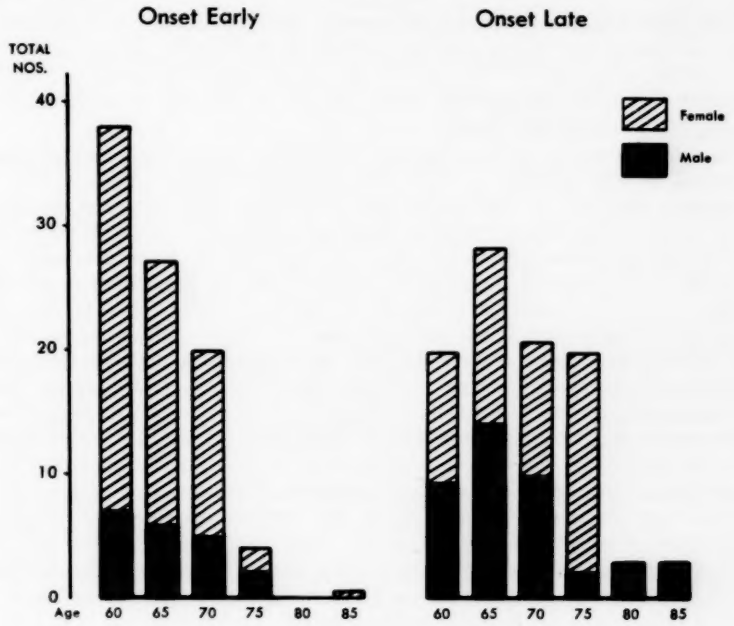


Fig. 1.—First admission rates for schizophrenia and manic-depressive reaction per million home population. By permission of the Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service (46).

utive series studied at one mental hospital by Dr. Kay and myself shows a substantial incidence of affective psychoses commencing in late life (Figure 2). Moreover, the reversal of the pattern observed in schizophrenia is complete, for in advanced age the men overtake the women.

For this most severe and incapacitating form of depressive illness alone, the morbidity risk in the general population is approximately one per cent for men and almost twice as great for women (1, 2). As there are reasons to believe that those predisposed to fall ill in this way number several times this calculated expectation, that is, from 4 to 8 per cent, we deal with one of the commonest maladies of human beings. In so far as disorders partly determined by single monohybrid genes are concerned, manic-depressive psychosis is probably the commonest illness of its kind known to man.



Age & Sex Distribution in Two Groups Aged 60 & Over with Affective Disorder

Fig. 2

Any attempt to formulate aetiological theories from the clinical facts must therefore take account of this association of depressive states in their severe form with the female sex and with late middle and old age; it must also reckon with its extraordinary frequency.

'Endogenous' and 'Reactive' Depression

We need not long delay over the clinical features of typical endogenous depression. There is the relatively rapid and often step-like onset of an all-pervading sadness and despair which gives a painful taint to all activities, linked with a sense of failure and inadequacy, feelings of guilt and self-reproach and imaginary misdemeanours. The contempt and derision read into other people's behaviour and the diseases with which the patient imagines he is afflicted are a just punishment for his misdeeds; poverty, disgrace and, in our culture, damnation in hell lie ahead for his family as for himself; retardation to the point of stupor or agitation with an agonizing restlessness, purposeless over-activity or a combination of the two may be seen. Instead of depression, apathy and inertia or severe anxiety may dominate the picture in the agitated cases and is often the cause of much of the patient's histrionic and importunate behaviour. This is prone to occur at night or in the early morning when behaviour may assume a panic-like intensity.

More dangerous are the mild and more subtle forms of the disorder which often steal on the patient imperceptibly and rob him of spontaneity and initiative. Work, speech and personal relations lose the stamp of his individuality, he becomes aware of an all-pervading dullness, infecting all that he does, rendering him slow,

indecisive, dilatory and ineffectual. Renewed efforts at fulfilling obligations are doomed to failure, and it is in this sort of state of mind at the beginning or in the recovery stage of depressive illness and in the very deceptive so-called "smiling" depressions, where the gulf between intention and act can still be bridged, that so many suicidal attempts are made.

It would be out of place in a setting such as this to give more detailed clinical descriptions. I wish merely to stress the frequency of physical symptoms such as headache, tinnitus, aching in the chest, dyspepsia, constipation elaborated by a self-scrutinizing hypochondriasis, paranoid delusions and more rarely nowadays, of hallucinations in tune with the depressive affect. An appearance of ill-health and senescence can descend with the onset of a depression in a matter of weeks on a robust individual in her or his prime, and often leads to expensive, long drawn-out, futile investigations. In one study carried out in general practice(3), it was found that 40 per cent of patients with depression had presented with symptoms more or less suggestive of organic disease, yet in such patients, symptoms like exhaustion, loss of interest, failure of concentration and inability to cope with life were rare in the extreme as presenting complaints of organic disease.

Those who regard endogenous depression as a relatively distinct entity rather than an extreme version of the normal responses of sadness, grief and mourning, emphasize certain features as constituting the essential hallmarks of this family of conditions.

(*a*) A quality of affect which many intelligent and discerning patients are able to attest is different in kind from their normal despondency, which relatives will insist is outside the range of their ordinary affective responses and which to the psychiatrists who uphold this view seems difficult to probe or understand by empathy. The patient often differentiates between the illness and the emotional reactions peculiar to him (14).

(*b*) The patient's experiences, disabilities, behaviour as a whole, seem out of character with his previous personality, representing a break in continuity with previous conduct and therefore often incomprehensible to those close to him. The premorbid personality is relatively well-adjusted in contrast to that of neurotic depression, which is emotionally unstable or psychopathic, although there is inevitably an overlap between the two phenomena in this respect.

(*c*) Although it may have followed stress or misfortune, the response seems disproportionate to what has preceded it and long outlasts the duration of adverse circumstances or subsides even though these remain unchanged. Those who have recently stressed the so-called reactive character of many endogenous depressions have forgotten the example Kraepelin quoted many years ago of the woman who fell ill in a first attack after the death of her husband, a second after the death of her dog, and a third after the death of her dove.

(*d*) There is a characteristic diurnal variation and sleep disturbance in endogenous cases, the most severe depression occurring after early morning awakening and lifting as the day progresses.

(*e*) There is an invariability of affect, an unresponsiveness to changes in the environment and in circumstances.

Some 25 years ago Aubrey Lewis, in a succession of erudite and influential papers on depressive states (3, 4), concluded that there were no reliable criteria to differentiate so-called endogenous from reactive depressions, and that such differences as had been described were so subject to individual interpretation as to be virtually useless. He contested the widely held notion that reactivity and psychogenesis were identical, or that hereditary and environmental components of the clinical picture could be distinguished.

TABLE 1
Status of cases of endogenous and 'reactive' depression within two weeks of completion of ECT

	Symptom-free	Improved with mild residual symptoms	Improved with marked residual symptoms
Endogenous depression	45	12	7
'Reactive' depression	3	9	9

Chi-square = 21.07, Df = 2, $P < 0.01$.

A similar position had been previously taken by Mapother (5), Lewis's predecessor at the Maudsley hospital, and subsequently by writers with psychobiological orientation such as Muncie (6) and Whitehorn, and during the Second World War by Curran and Mallinson (7) and Tredgold (8). Gillespie (9) and Rogerson (10) took an opposite view, holding that the distinction was both real and of practical value.

It may be agreed that the presence or absence of a precipitant for the illness is of dubious value as a basis for the classification of depressive states. For even when the most stringent criteria are applied in assessing the validity of apparent precipitating factors, many indubitably endogenous depressions are "reactive", but only if all quantitative considerations are omitted. Moreover, it is in the wider sense of an affective responsiveness to outside influences that many workers favouring the distinction have used the term "reactive."

None of the terms 'reactive,' 'neurotic,' 'psychopathic' or indeed 'endogenous' are unexceptionable, and yet the observations of the past 25 years in which treatments have been available as a therapeutic test have on the whole substantiated the validity of the distinction implied. Many of those who have made a special study of physical treatments in psychiatry (11, 12, 13) have stressed the difference in quality and duration of response to convulsive treatment, and in the investigations of the effects of prefrontal leucotomy carried out by Partridge (14) in 1949 and more recently by Elithorn and Slater (15), this difference in the response of the endogenous and reactive depressions was strikingly plain. In an investigation of the effects of ECT, we found the same difference in the results. The immediate result was less satisfactory and the rate of relapse higher in the 'neurotic' group (Tables 1 and 2).

It is noteworthy that in a recent investigation, after concluding that there was no essential difference between so-called endogenous and neurotic depression on the basis of reactivity or hereditary loading, Garmany (16) discovered retrospectively

TABLE 2
Status of cases of endogenous and 'reactive' depression six months after end of ECT

	Well or improved	Relapsed
Endogenous depression	49	15
'Reactive' depression	14	7

that he had selected ECT as the treatment for the cases he had identified as endogenous depression in the majority of instances, but only in a negligible proportion of the neurotic group. He rationalized his choice by saying that this merely reflected a judgment that in the neurotic cases the depression, while identical with endogenous cases in all other respects, was more superficial. If so, it should have been all the more readily dispelled by electroplexy. The choice of different treatments for the two groups invalidates the conclusion reached that they were identical.

Needless to say it is not possible unequivocally to allocate every case to one or another class of depressions; such perfect classificatory systems exist only in heaven. But provided the evidence about the patient's personality development and adjustment is correlated with the clinical findings and the facts are 'weighed with judgment and insight,' most depressive illnesses can be diagnosed as endogenous or neurotic. The cyclothymic individual knows at once what is meant by endogenous mood change and the diurnal variation in affect is likewise familiar to him. This sort of mood will be found on careful inquiry to be unknown to the neurotic patient whose previous affective surges have almost invariably been responses to adverse circumstances (47). The responsiveness, the characteristic sleep-rhythm and the factors already stressed above will further serve to establish the diagnosis.

It would indeed be strange if there were a continuous gradation from normal sadness, which is a universal experience, to the affective change characteristic of the melancholic. For in the case of the latter, there is a great deal of evidence to suggest that the genetic predisposition is a specific one due to a single monohybrid dominant gene of variable expression (18). On the other hand, in the case of mood changes varying only in degree of severity from the norm, we deal with differences in the responsiveness of graded human attributes, for which any hereditary basis is probably of a quite different kind (19).

Thus the experience of the past few decades has on the whole upheld the view of traditional German psychiatry as against those who have favoured the unity of all forms of depressive illness. This does not preclude the possibility of ultimately embracing all forms of depressive reaction in terms of some unifying psychological or physiological concept. An interesting hypothesis of this kind was put forward some years ago by Ewen Cameron (20). For the time being, however, it seems unjustified to ignore in practice or scientific enquiry the distinction between neurotic and endogenous types of depression.

Depression, Anxiety and Depersonalization

One of the major problems in relation to the phenomenology of depressive states is their differentiation from states of anxiety. Anxiety is often a prominent feature in depressive states, although this is commonly inferred from behaviour rather than from the patients' complaints. A number of authors have claimed that there is no clear or logically consistent dividing line between anxiety states and depressions, and Lewis (3), in his influential paper of 1934, did much to advance the conception of the anxiety state as a form of affective disorder which merges insensibly with conditions dominated by a mood of sadness. His description of the person with depression as one unhappy and ill with his unhappiness would clearly embrace endogenous and reactive depressions and anxiety states. In a more recent account by him the relationship was described as one between two types of depression, melancholia and agitated depression, each with a corresponding minor variant, simple or neurasthenic depression for the former and anxiety state for the latter (21). More general agreement seems to exist that in so far as there is such a thing as a neurotic as distinct from a psychotic form of depressive illness, it is more or less coloured by anxiety and indistinct from anxiety states proper. Thus Har-

rowes (22) included in a description of psychoneurotic depression, anxiety of 'all three shades, inquiétude, anxiété and angoisse.'

Experience with ECT speaks against the unity of all forms of affective disorder; endogenous depressions usually benefit, whether agitated or not, whereas anxiety states fail to respond or get worse (13). In many patients a lasting terror of this form of treatment is conferred. This was a common effect of ECT on patients suffering from a form of neurotic illness with prominent anxiety that we have studied. In fifteen of twenty-four patients so treated the symptoms were aggravated. The clinical picture of this disorder is dominated by anxiety, depersonalization and depression. Reactive and endogenous depression are probably the commonest among a wide range of diagnostic labels that are attached to it. It is relatively common and if it is a distinct entity, as we believe, its differentiation may help in the establishment of a more clear and acceptable classification of depressive illness and of psychoneurotic disorders as a whole. We have found this condition to be a far commoner setting for depersonalization than is endogenous depression, schizophrenia or other neurotic disorders, and I should like therefore to describe the results of an investigation of a series of 135 cases, together with 50 controls suffering from other neuroses and 50 others in hospital recovering from a recent physical illness (48).

Over two-thirds were women and although the commonest age of onset was in the late twenties, there was an unexpectedly high proportion of cases with first breakdown occurring after the age of 45. The association with calamitous circumstances was consistent and striking. The illness almost invariably followed closely on a bereavement or suddenly-developing serious illness in a close relative or friend (37 per cent), illness in or acute danger to the patient himself (31 per cent), and frequently severance of family ties or acute domestic stress, which often constituted a threat to marriage (15 per cent) (Table 3). Thus in 83 per cent of the cases the illness was consequent upon circumstances of a painful or disastrous nature; illness was numerically more important among the men and especially among the older patients, and bereavement among the women. Some examples of precipitating

TABLE 3

Precipitating causes in 150 cases of the phobic anxiety-depersonalization syndrome as compared with those in 50 neurotic controls (+ indicates a statistically significant difference from neurotic controls)

	Male %		Female %	
	P.D. cases	Neurotic controls	P.D. cases	Neurotic controls
Bereavement or serious illness in close relatives	30+	4.2	35.5+	3.8
Illness in or danger to patient	50+	20.8	19.6	23.1
Calamity, including severe frights	—	—	4.7	—
Severance of close ties	2.5	4.2	7.5	7.7
Domestic stress, including marital disharmony	—	8.3	6.5	11.5
Childbirth and pregnancy	—	—	13.1	3.8
Faints	5.0	—	6.5	—
Anaesthetics	—	4.2	—	3.8
Head injury	7.5	4.2	2.8	3.8
ECT	—	—	.93	—
Strife outside family circle	2.5	—	—	—
Sex trauma	—	4.2	—	—
Not known	2.5+	50.0	2.8+	42.3

events were: a girl of 21 discovering during the night that her aunt was dead in bed beside her; a young mother finding her child in status epilepticus from which she subsequently died; a child of 14 witnessing her father's massive haematemesis; and a nervous obsessional workman seeing his mate collapse and die from a coronary thrombosis and finding an hour later the man's false teeth in his pocket.

From the point of view of the aetiology and physiopathology of the condition, considerable interest attaches to the small minority of cases in which accidental or induced change in the level of consciousness, often of a slight or transient character, seemed to initiate the illness. Such changes included spontaneous syncopal attacks, and in some cases relatively slight head injuries.

Following the abrupt onset, a small proportion of cases showed an acute delirious phase or a short period of clouded consciousness which subsided to reveal the unreality feelings — a distressing awareness of some change in the self, a negative transfiguration of the outer world, an incessant and compelling self-scrutiny, and an oppressive sense of loss of all spontaneity in movement, thought and feeling associated with a subjective sense of automaton-like behaviour — of being passive spectators of one's own activities. Invariably associated with this picture in the chronic stage of the neurosis was a characteristic pattern of phobic anxiety — a fear of being alone in the streets, of entering crowded rooms, of waiting in shops in queues, which provoked a fear of falling or fainting, losing control, making a scene, being seen helpless, all possibilities which seemed strangely distressing to these patients. The clinical picture was dominated sometimes by depersonalization and at other times by this phobic pattern.

Associated with this essential core of the illness there was a rich symptomatology. Hysterical conversion symptoms were relatively frequent. One-third of the cases suffered feelings of faintness, giddiness or one or a succession of actual faints (the difference from a group of mixed neuroses being statistically significant). In almost 40 per cent of cases there were not only unreality feelings, sometimes of an episodic nature, and *déjà vu* phenomena, but additional symptoms suggestive of dysfunction of the temporal lobes or related structures in the limbic system. These included metamorphopsia, panoramic memory, intense hypnogogic hallucinations and the interesting closed eye hallucinations ('private cinema phenomenon') often described in experiments with hallucinogenic drugs and in predelirious states. Severe tension and vasomotor disturbances were common, and also an intense, brooding gloom with neurotic features (44 per cent). However, in about 10 per cent of cases the condition bore some resemblance to an endogenous depression. Hypochondriasis (61 per cent) and obsessional symptoms (66 per cent) were also frequently elicited. The picture could thus be described as a 'pan-neurosis'. In a proportion of cases schizophrenic-like symptoms were observed, but only during short-lived bouts of illness marked by clouding of consciousness, hallucinations and delusions, a strong depressive colouring, or all of these features. For these reasons, and in the light of follow-up studies in a group of such cases, I believe we are likely to be dealing with a relatively benign condition on the borderlands of schizophrenia and allied perhaps to such conditions as the short-lived schizophreniform states of battle or other acute emotional stress, and the symptoms induced by hallucinogens.

A comparison of the previous personality of the patients with that of control groups helped to define reasons for their vulnerability to the stresses to which they had been exposed. They proved to be on the one hand conscientious, scrupulous, earnest, routine-bound and anxiety-prone — in other words mildly obsessional — while on the other hand they were dependent and emotionally immature to a marked degree (the relationship with their mothers in particular being close), intense, and often exclusive of social contact outside the immediate family circle. Deprivation of parental care and affection had been no more common than in

the control groups; the majority had been brought up in happy and united families. They had betrayed relatively little sign of maladjustment before the onset of their illness other than mild childhood phobias and slightly more physical ill-health than was found in the control groups. Adjustment at school and at work had been relatively good, but an interesting finding was the high incidence (60 per cent) of total frigidity among the women and frigidity of many years' duration since a first or second childbirth in a further 16 per cent. The difference from other groups was highly significant. Yet investigations revealed that the women achieved marriage significantly more often than the general population of comparable age, and the proportion of single women among them was lower than expected by chance. Despite this, the proportion of failed marriages was relatively low, and as only a minority had attained an adult pattern of sexuality, the evidence suggested that these women had sought marriage for security and had striven to maintain their marriage ties. The men proved to be a representative sample of the general population with respect to their marital status, possibly because they were more likely than women to regard marriage as an added burden rather than a refuge. Such dependent rigid individuals with a craving for security would be expected to be disturbed by circumstances of a calamitous nature.

However among the older patients there were many vigorous and effective individuals and even an inflexible dependent personality does not wholly explain an abrupt, step-like change to a form of disability that has the stamp of a specific cerebral disturbance upon it, with its clouded state at onset in some cases, syncopal attacks in others, temporal lobe features in two-fifths of cases, as also the abrupt disappearance or amelioration of symptoms in a high proportion of cases in the course of controlled trials that we have been conducting for a form of pharmacological treatment. The precipitating factor again plays some part in causation but is neither an adequate nor a wholly necessary cause.

The only way in which depersonalization may be evoked at will is by the administration of hallucinogenic drugs or by stimulation of the cortex. In each case some change in level of awareness is involved, although this may be of an exceedingly subtle nature. When, as in the phobic anxiety-depersonalization syndrome, we find disturbances in the integration of perceptual experience, disturbances of affect and of the temporal sequence of events, as well as other phenomena hinting at a dysfunction of the limbic system, I believe that we are likely to be dealing with some chronic disturbance of the mechanisms regulating awareness; perhaps one of those step-like gradations of consciousness with which, at deeper

TABLE 4

Varieties of chronic illness (excluding sensory defects) in two groups with affective disorders (figures are percentages showing proportions of affected individuals in each group)

	Cardio-vascular disease		Uro-genital disease		Other conditions, e.g. lung, C.N.S. and neoplastic diseases		Multiple disabilities		Total incidence	
	M	F	M	F	M	F	M	F	M	F
Early-onset group	11	10	4	10	22	14	7	5	28	33
Late-onset group	22	15	18	10	40	21	24	10	57	37

levels, we are familiar in the patterns of delirium and irreversible coma. Such a hypothesis has the merit of meaningfully linking the three modes of onset defined in the condition, namely calamity, physical illness and syncope. Some degree of clouding of consciousness is relatively common in states of intense fear. Such clouding, and in many cases the full pattern of illness described here, may be distinguished in some of the classical accounts of 'fright neurosis' given by writers on this subject during and after the First World War.

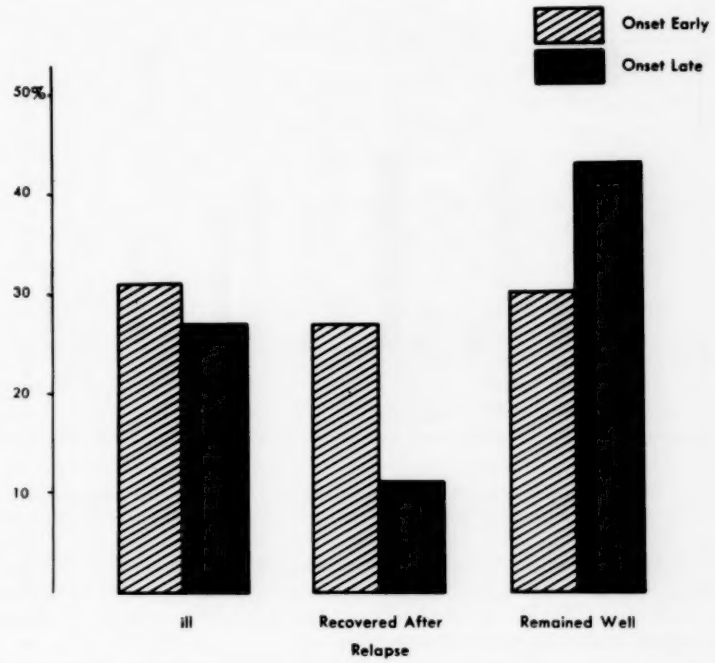
In brief, therefore, we have in this condition an acute psychological or physical stress impinging upon an Achilles heel in predisposed individuals and leading to some subtle and specific disturbance of cerebral function with severe anxiety and depression, depersonalization and some derangement of the regulation of awareness. The relationship between changes in level of consciousness and disturbance of affect is a subject which has received little systematic exploration, although as I shall have occasion to indicate later, it arises in relation to a number of important psychiatric disorders.

Variation with Age

The concept of a specific involutional pattern of endogenous depression characterized by anxiety, restlessness and agitation, bizarre hypochondriasis and grandiose, nihilistic and paranoid delusions occurring in the setting of a meticulous, rigid, inhibited (23) or over-anxious, timid, sensitive (24) personality, is no longer tenable in the light of the investigation of Lewis (3) and more recently Tait, Harper and McClatchey (25) and Stenstedt (18).

Yet there is evidence that some differences with age do appear in relation to certain characteristics of depressive illness. Evidence obtained by Dr. David Kay working first at Graylingwell Hospital and later in Professor Sjögren's unit in Stockholm has shown that the important group of individuals who fall ill with depressive illness for the first time in old age have a smaller hereditary loading with affective psychosis in their families than depressives falling ill in earlier life (49). Correspondingly, exogenous factors such as physical illness, usually pursuing a chronic course, are commoner and probably of some causal importance (Table 4). It will be seen that all kinds of physical illness are commoner in those patients with late onset, and in males in particular, as compared with old people whose illness had commenced earlier in life (50). Bereavement has also been found more commonly as a precipitating factor among cases with depressive illness of late onset than among those who have also had attacks in early life. The symptoms of physical illness are all too easily overlooked, overshadowed as they are by the patient's gloom and despair and frequent hypochondriasis, and it is a good rule to look for an associated physical illness when a depressive psychosis appears *de novo* in old age. These patients hold their recoveries following electroplexy in a relatively stable manner (Figure 3) and neurotic traits are less common among them than among those who first become depressed before the age of 60 (26).

We deal then with a relatively stable and well-integrated group of individuals in whom breakdown is avoided during most of the life span, occurring only when they are afflicted by physical ill-health or other vicissitudes in old age. Are we dealing in these old people, whose depressions were accompanied by physical illness, with a symptomatic psychosis? Although physical illness was common (in 43 per cent of the men and more than half the women), the depression had arisen without it. Moreover, the physical and psychiatric illnesses seem to run relatively independent courses; many cases continue to suffer from physical disabilities, but the depression recovers with treatment, and the opposite is also true. Decline in physical health is thus neither an adequate nor a necessary cause. But clearly



Psychiatric Condition in Two Groups with Affective Disorder 9-27 Months after Admission

Fig. 3.—By permission of the Journal of Mental Science.

physical disability is a contributory factor of importance and seemingly of special significance in relation to men.

In the classical accounts of mental disorder in old age (27, 28), presenile and arteriosclerotic psychoses alone are discussed and senescent depressive and paranoid states are freely attributed to underlying cerebral disease. Even the literature of two to three decades ago stresses the difficulty of differentiating beyond the forties between depression caused by cerebro-vascular disease and endogenous depressive illness (3), and before the advent of electroplexy depression was freely attributed to an associated hypertension, even when evidence for cerebral infarction was wholly lacking. However, the confusing overlap in the old accounts between paranoid states, depressive and delirious syndromes, and the manifestations of gross or advanced cerebral disease, which probably led Kraepelin to declare that old-age mental disorder was one of the darkest chapters of psychiatry, is not upheld by recent observations (51). Figure 4 shows that each of the groups into which patients were classified on the basis of the presenting clinical picture has a distinctive pattern of outcome which is independent of age differences to a considerable extent. In a follow-up study seven years after admission, differences between these five groups were still conspicuous. Each case with sustained depressive (or manic) symptoms not associated with unequivocal neurological signs of cerebral infarction was placed in this study in the depressive group. Yet the incidence of dementia and other features indicative of cerebral disease was no greater at follow-up in those whose first depressive

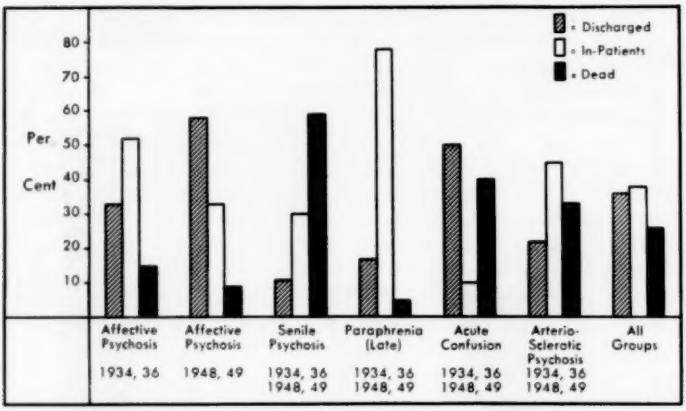


Fig. 4.—The status of 450 patients aged 60 years and over 6 months after admission to a mental hospital in the years 1934, 1936, 1948 and 1949. By permission of the Journal of Mental Science.

attack had appeared after the age of 60 years than in patients who had also suffered from depression before this age. And in each group only a relatively small proportion were thus affected (26). The previous history and subsequent course of both depressive and organic cases suggest that even when we are confronted with those intensely unhappy and hopeless old people — seemingly beyond caring about the world, unconcerned with what is happening around them, feeble, retarded, senile in appearance and often physically ill — we deal more often than not with a potentially recoverable illness.

Clouding of Consciousness and Depressive Illness

In clinical practice, some of the most florid and dramatic depressive symptoms are seen in a setting of some clouding of consciousness. Some of these cases follow an acute physical illness or some surgical procedure which involves anaesthesia, although the psychosis long outlives any objective indications of metabolic disturbance. These cases are given varying interpretations, being regarded as symptomatic psychoses by some psychiatrists, and by others as variants of endogenous depression in predisposed individuals, triggered by a derangement of metabolism. Each of these views has a germ of truth. Thus the clouding of consciousness is associated in some cases with disturbances in the EEG (29), and this tends to confirm that an organic factor does indeed play some part in causation. On the other hand these cases behave like ordinary endogenous depressions in their response to ECT, and in my experience carry a very good prognosis. But one should not lightly class with manic depressive psychosis, or even with a broader group of endogenous depressions, cases with clouding of consciousness and electroencephalographic abnormalities. Hence neither of the conventional views about the nosological status of these cases is wholly satisfactory. I believe that it is fruitful to give separate consideration as a group to psychotic illnesses resembling the affective or schizophrenic disorders, but associated with clouding of consciousness. As far as I know, this subject has nowhere been given separate treatment, although the disorders grouped in this way have certain interesting features in common. The field is a large one, and includes the short-lived psychotic depressions and paranoid states of epileptics, the surges of de-

pression in alcoholic intoxication, the oneiroid psychoses of Mayer-Gross (17) which were recently discussed under the heading of oneirophrenia by Meduna (30), other members of the schizophreniform group in which both clouding of consciousness and a depressive colouring are common, the periodic catatonias of Gjessing (31, 32) in which the same features are often manifest, the psychotic-like states induced by hallucinogens, and the florid melancholias associated with physical illness described above.

There is a marked tendency for these conditions to have both affective and schizophrenia-like components. This emerges clearly from the descriptions of oneiroid cases given by Mayer-Gross and Meduna. This is also a feature of the periodic catatonic, in which some blunting of awareness as well as EEG abnormalities have been demonstrated (33, 34). In the mood changes of abrupt onset common in epileptic states, complex and systematized paranoid experiences are frequent; it is interesting that the clouding of consciousness may be subtle in these cases and difficult or impossible to demonstrate by clinical examination. A depressive colouring is likewise frequent in the acute schizophreniform psychoses observed during battle stress and in the psychogenic psychoses in general (35). Although it is the schizophrenia-like features induced by mescaline and LSD that have received most attention in recent years, it has been known since the earliest observations (36) that affective changes are equally prominent. It is noteworthy also that in the psychotic reactions induced by ACTH and cortisone, frequently associated with some clouding of consciousness, the picture may be a predominantly affective one with elation or depression, but paranoid hallucinatory features are quite often associated. The blunting of awareness in these cases is often elusive, transient or intermittent, although a temporary disturbance of cerebral function can sometimes be demonstrated with the aid of electroencephalography. We have recently studied two cases of a florid depressive psychosis, one with a marked paranoid colouring, the other with perplexity, incongruity of affect and imperative hallucinations; the illness was associated in each patient with mitral stenosis. In the latter, clouding was suspected but not conclusively demonstrated by means of clinical examination. However the EEG in one case (Figure 5) confirmed the presence of a slight blunting of awareness. He was treated with chlorpromazine and the EEG abnormality subsided, with a corresponding recovery from the psychosis within a week.

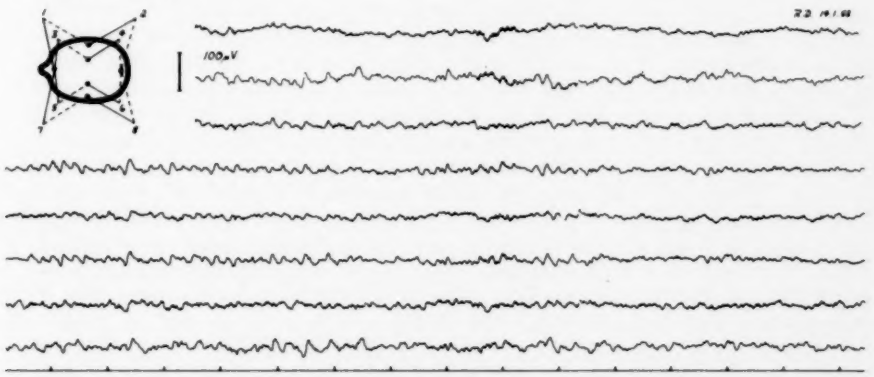


Fig. 5.—The EEG in a case of mitral stenosis with depression, ideas of guilt and unworthiness, and suicidal ruminations. No definite clouding, orientation correct, but marked retardation and indecision. The EEG shows symmetrical diffuse theta activity with some low-voltage delta components. The rhythms dominate the record. Psychosis and the EEG disturbance subsided together in a week.

In many of the conditions described, an exogenous toxic or organic cause is present, and the obvious explanation is that these are toxic confusional states rather than disorders having any kinship with 'functional' psychoses. Even if this were the case, it would be short-sighted to overlook the resemblances to which attention has been drawn. Moreover the associations between states of impaired awareness and a 'mixed' psychotic picture are independent of toxic factors in the ordinary sense, being observed also in epilepsy, oneiroid states, the short-lived psychoses of battle stress and in the transient, acute psychotic episodes we have observed in the course of a small proportion of cases of the phobic anxiety-depersonalization syndrome.

Genetic data would clearly throw valuable light on the kinship of such atypical psychoses with the manic-depressive and schizophrenic groups which they resemble. Unfortunately evidence is very scanty on this point. Leonhard (37, 38) has adduced some evidence that there are clinically atypical forms of schizophrenia, often with acute onset and a marked depressive colouring, which carry a better prognosis than the general run of cases, and he finds these to be genetically distinct. If we can regard alcoholic hallucinosis, long believed to have some kinship with schizophrenia but often associated with subtle disturbances of awareness and some depressive features, as presenting similar problems to those of the illnesses discussed above, we have the interesting suggestions offered by a recent study carried out by Benedetti (39). The genetic loading of the relatives of these cases with schizophrenia was considerably less than that in the relatives of schizophrenics proper. More surprisingly, those terminating with schizophrenia-like deterioration were found to have relatively little hereditary taint with schizophrenia, while cases ending with a chronic organic picture showed rather more.

It seems undeniable that under certain conditions disorders with a resemblance to schizophrenia and manic-depressive psychosis may appear in a range of individuals drawn from a less vulnerable population than those specifically predisposed to affective psychoses and schizophrenia. These conditions are created in some instances by toxic effects, or in association with a presumed disturbance of cerebral function; but the crucial point is that in many of these cases, the latter could not be inferred from the clinical psychiatric examination alone. The only factor held in common by all the disorders listed is a subtle impairment of consciousness evoked by an epileptiform discharge, a psychogenically induced, intense affective disturbance (as in the battle stress psychoses and in the short-lived psychotic episodes of our depersonalized cases), or by some exogenous toxin. One would expect the psychoses of such less vulnerable individuals to carry a relatively benign prognosis. Here again there have been few studies, but the psychotic disturbances of epileptics are usually short-lived, as are those induced by battle stress. The depressive surges of alcoholics, which so often lead to suicidal attempts, subside with recovery of normal awareness, frequently with partial or complete retrograde amnesia. Periodic schizophrenias are generally agreed to be relatively benign, and clouding of consciousness in schizophrenia is a good prognostic sign (40). I know of no comparable study in depressive psychoses, but in the material we have investigated of melancholias with clouding, the response has been uniformly good. In oneirophrenia, according to Meduna (30), the response to ECT, unlike that in schizophrenia proper, is favourable and lasting.

It seems to me that these facts warrant two tentative conclusions each of which requires further exploration. The first is that individuals in whom a depressive or schizophrenic psychotic picture is seen in the setting of clouding of consciousness are not drawn from the same population as the main body of cases of these forms of mental illness. The second is that subtle states of clouding of consciousness are in some way aetiologically bound up with a proportion of cases of psychotic illness;

perhaps a state of blunted awareness widens the range of individuals who can manifest psychosis beyond those who are constitutionally predisposed, the clouding acting in some way as a catalyst of psychotic process. In a quite different context, the interesting experiments of Weinstein and Kahn (41) on the reappearance of anosognosia for hemiplegia following the intravenous injection of thiopentone will perhaps provide some indication of the sort of facilitation that I have in mind.

Hypochondriasis and Affective Disorder

An unpleasant and disabling preoccupation with bodily sensations or with health, for which there is no objective justification, is generally believed to occur in a wide variety of clinical settings. In a mild form it may be induced commercially or iatrogenically, it may be a feature of anxiety neurosis, hysteria, schizophrenia, depression, mania or an obsessional state. The obsessional personality is generally agreed to provide a fertile breeding ground for hypochondriacal preoccupations as its ruminative tendencies are prone to cause a compelling self-scrutiny in the presence of mild bodily malaise. Susceptibility tends to increase with advancing age (17). However, it is with the relationship between hypochondriasis and depressive states that we are specially concerned here. This has been in dispute for some centuries and the issue is still not quite decided. Of the two most influential authorities writing on the subject in recent years, Lewis (3) adopted the standpoint which had been that of Bleuler and Griesinger before him, that a depressive mood was the essential basis for the development of delusional hypochondriacal ideas. The usual blend of depression and anxiety in affective psychoses was frequently associated with coenaesthetic disturbances and the attention directed to these initiated the process of hypochondriacal self-scrutiny. He denied that any clear distinction between different types of hypochondriasis could be made from the nature of the accompanying affect. Gillespie on the other hand adopted an opposite view, holding that hypochondriasis existed as an independent entity in which overt anxiety was absent and any depression was of a purely secondary kind. He drew attention to the bland complacency with which some of these patients, particularly the women, described their symptoms. This 'belle indifférence' he interpreted as indicative of a motivated flight to illness and of the predominantly hysterical aetiology of hypochondriasis in the female sex.

A quarter of a century of observation and experience with physical treatments separates us from these papers. Two points can be made in relation to this controversy which, I believe, would now command a wide consensus among practising clinicians. The first is that where hypochondriacal symptoms are the presenting disability and dominate the clinical picture, the natural course is almost invariably malign, showing no tendency to recovery, remission or even improvement, and often the reverse. One can hardly regard a course such as this as consistent with affective disorder. Secondly, where hypochondriasis is in the forefront without corresponding affective disturbance, electro-convulsive treatment is either without effect or of such transient benefit as to be therapeutically worthless. In so far as experience with physical treatments has thrown light on the situation, it has therefore tended to confirm the independence of a group of cases with prominent hypochondriacal symptoms from the affective psychoses proper.

Middle life may usher in an exacerbation of lifelong preoccupations with somatic sensations but hypochondriasis may also develop at this age within a relatively short time, and even abruptly, in individuals (more commonly women than men) who have previously often been stable, effective, energetic and masterful. Health may have given little trouble previously, but following an operation, or perhaps extraction of a few teeth, or without any such trigger, a process of somatic self-scrutiny begins which soon succeeds in excavating complex and bizarre sen-

sations that are described in intricate detail. The various interpretations of these experiences are held with more or less delusional force, but depressive colouring is slight, variable or absent, and overt anxiety uncommon. The bland unconcern which Gillespie described in his female cases and at times even an incongruous levity may be manifest. Yet it is difficult to accept a diagnosis of hysteria for a malady that commences in middle life, rarely with previous symptoms, for which convincing motivation is not to be found, and which pursues a chronic course without remission, improvement, or any change in the form of expression of the symptoms. Despite their assets as personalities many such patients impress one as emotionally shallow and opinionated. A serious or acute physical illness seems to exert a devastating effect. Their mortal, vulnerable bodies seem to have been forced upon the attention of these patients as if for the first time; during an acute respiratory infection there may have been some extra-systoles or bronchospasm, and now "the heart pounds in the head," and "the air won't go all the way down the chest," "the bones in the neck creak and send electric sensations into the head," and no energetic or decisive action, such as that which has formerly surmounted obstacles, is of any avail.

A less common setting for hypochondriacal symptoms among women in early or late middle-age is a syndrome we have recently investigated (42). These are women usually in the fourth or fifth decade who look prematurely old and may have had an early menopause. There is amenorrhaea or oligomenorrhaea, anergia and lassitude, loss of libido, a fluctuating shallow depression and a hypochondriacal preoccupation with various bodily discomforts. In three of the 12 cases studied there were phobic symptoms. Complaints of abdominal pain are particularly frequent. There is intense sensitivity to cold, and on examination absent or markedly diminished axillary and pubic hair, and dry, shiny, tight, yellowish skin, sometimes patchily pigmented. Urinary 17-ketosteroids are 2 mg or less per 24 hours, the glucose tolerance curve is flat and there may be heightened insulin sensitivity. Some of our cases had been previously treated with ECT with no effect or an exacerbation of symptoms. We are clearly dealing with some endocrine deficiency, possibly a mild hypopituitarism, although there is at present no indication as to what the cause of this might be. However, the two cases we have been able to treat with ACTH followed by hydrocortisone, stilboestrol and thyroid have shown a striking improvement.

The proclivity of athletes for developing mild hypochondriacal symptoms is well recognized. A caricature of this situation is provided by those individuals, usually male, who have invested immense effort in and attached an exaggerated importance to the cultivation of bodily prowess, which often comes to dominate their whole life. These are the addicts of chest expanders, the aspirants to fame in 'Mr. Atlas' competitions, the patrons of the 'you too can have a body like mine' business. There is often some simple psychological starting point in childhood such as a physical disability or deficiency or strong feelings of inferiority. At the onset of some illness, the advent of signs of aging in middle life, an accident or operation (in one of our cases after the wife had given birth to a stillborn child), these individuals may lapse into a chronic hypochondriacal self-preoccupation. It is interesting that despite the obvious psychological antecedents of this 'Mr. Atlas' syndrome, psychotherapy is as ineffective as in the other varieties of hypochondriasis, nor are any of the physical treatments to date of any value.

The relative incidence of the different forms of primary and secondary hypochondriasis is not known and a systematic re-examination of the whole subject is long overdue. My impression for what it is worth is that the most common is the primary hypochondriasis of women and that it is relatively distinct from hypochondriacal symptoms in a setting of affective disorder.

Depression and Obsession

The relationship between the depressive and obsessional groups of disorders is a complex subject and I can only touch on what seem to me to be a few crucial points.

Since psychiatrists have been dealing during the past few decades with an increasingly wide range of mental disorders, the proportion of cases with a typical cyclothymic personality has probably declined and I should be inclined to agree with Jarvis (43) that one of the patterns which one sees at least as often is that of the driving, conscientious, fastidious individual with high goals and aspirations often leading to a sense of failure and inadequacy, despite relatively high attainments. Whether or not this is the case can be reliably settled only by means of systematic surveys of clinical material which are currently out of fashion but which provide the only means of approach to many of the vital questions of psychiatry.

Minor obsessional thoughts, ruminations and compulsions are common in depressive states as a whole, and in markedly obsessional personalities more severe symptoms are regularly released by the advent of a melancholic affect, thus giving rise to one form of cyclical or recurrent obsessional state. These cases are rare, as also those in which such cyclical obsessional disorders occur in the setting of a non-obsessional personality. In both these groups the response to convulsive treatment is favourable. But in the majority of cases with obsessional symptoms predominant, the response to treatment is poor except that the depressive affect may be changed for the better, the obsessions remaining unchanged. For obsessions, as for hypochondriasis, paranoid symptoms and also depersonalization, one can formulate a general law: the more predominant any of these features is in relation to the affective disturbance, the further is the course and response to treatment likely to depart from those expected in depressive illness proper. And for all those examples there is a tendency to a kind of polarization of clinical features: where obsessions or hypochondriacal features are well to the fore, the depression very rarely impresses one as deep or intense, while with the affective disturbance dominant, obsessions tend to be mild, unobtrusive, and/or transient.

I should like in conclusion to touch on the subject of the change from obsessions to delusions. It is a by no means rare though little studied phenomenon for an obsessional syndrome to change into a psychotic one; insight is weakened, obsessional thoughts assume a compelling intensity, and the ability to struggle against the obsessional symptoms is undermined. The patient may now firmly believe he is polluted, that his neighbours are noting his smell and discussing his venereal infection; obscene thoughts are transformed into the hallucinatory voices of others; fear of aggressive behaviour changes into a conviction that cruelty or murder has been perpetrated. Such cases have been recently described in an interesting study by Rosen (44). It is customary to regard such cases, dominated most commonly by delusions, as schizophrenia; and the failure of such cases to regress and disintegrate in the manner schizophrenics do has been attributed by Stengel (45) to the rigidity of the obsessional personality structure. Rosen concurs in this view; yet his account makes it clear that the obsessional symptom pattern persists unchanged after the onset of 'schizophrenia;' the delusions and hallucinations commence almost invariably as outgrowths from the obsessional symptoms; long remissions are relatively common, and insight is partly or intermittently retained. Moreover, as Stengel pointed out, depressive symptoms are very common. I have found that the psychotic symptoms frequently recede over the years. The depressive hallucinatory and other psychotic symptoms may be dispelled for long periods by ECT, though the obsessions are unaffected. Schizophrenic personality change is very rare and the cases are not essentially different from those

many indubitably obsessional patients in whom a precarious hold on insight is temporarily loosened, or who have evanescent, psychotic episodes that rarely or never recur. I have had under observation eight such cases over a number of years and their natural history would appear to have more in common with that of obsessional states than with that of schizophrenia. These cases may of course be attenuated schizophrenics as Stengel suggests, but this remains to be substantiated, and the view that we are dealing with a mixed psychosis peculiar to obsessional states has meanwhile as much to commend it.

Conclusion

Emphasis has been laid in this report upon the differences among the various types of disorder in which depression of affect is manifest: differences between endogenous depressions on the one hand and neurotic depressions and anxiety states on the other, and differences among conditions dominated by hypochondriasis, obsessions, depersonalization and all these affective disturbances. In each case these distinctions have been insisted on and also denied for a considerable time, but experience during the era of physical treatments has, on the whole, upheld the views of those who have stressed the differences. This does not necessarily mean that no drug discovered in the future will violate the boundary lines as they are drawn at present. But in evaluating new drugs, it would be unwise to ignore them.

It seems to me that the most urgent need at the present time is for treatments in conditions such as the anxiety states, hypochondriasis, depersonalization syndromes and obsessional states, which admittedly have some ill-defined, remote kinship with affective psychosis, but in which we are without effective remedies. In contrast, a valuable treatment for endogenous depression is at our disposal in ECT. With regard to the latter, it is the problem of relapse in particular that detracts so seriously from the value of the treatment, a problem with which one hopes to obtain some help from advances in pharmacological treatment.

After discussing depressive disorder in so many settings, one feels compelled to give some consideration to the possible reasons for the ubiquity and universality of these reactions.

If we direct this question to the pathological variants of depression alone, we deal with disorders for which the expectation is in the neighbourhood of 2 per cent. Moreover, we must assume from the relatively low penetrance of the genetic factor in question that three or four times this number of individuals in the community at large must be vulnerable though they escape frank breakdown. It is difficult to regard a biological predisposition as frequent as this as wholly pathological; the equilibrium between mutation and selection is hardly likely to be established at such a high frequency for a predisposition which is wholly harmful. No conclusive answers can be given at the present time to the questions thus raised. The balance of the evidence does, however, suggest that manic-depressive psychosis is a disorder commoner in those segments of the population characterized by high attainment. There is also suggestive evidence of some relationship between the cyclothymic constitution and talents of an unusual or creative nature; and one does not have to search very hard for the social value of the many tenacious, fastidious, conscience-ridden people of high aspiration who bulk so large among the depressive illnesses.

Writing about mourning and melancholia in 1916, Freud pointed out that there was in both the same psychic pain, the same temporary inability to acquire a new love object, due in each case to a withdrawal of libido. In ordinary mourning, however, the attachment to the love object is less narcissistic and ambiguously poised; and at the release of libido and its re-absorption into the ego, the work of

mourning need consist only in gradually shedding the associations with the dead person. There is more to depression than grief, and Freud himself recognized the gulf between ordinary mourning and melancholia. But in so far as a link between the two exists, and mourning can be regarded as one constituent of the psychopathology of depression, it is clear that in the latter we deal with a type of response peculiar to the highest levels of evolutionary development. Moreover, the identifications from which the attitude of mourning stems would clearly tend to foster social cohesion and, as such, to carry survival value for the communities in which it evolved.

These are little better than guesses. They have been added only to underline that when dealing with a phenomenon as common as the depressive state, a broad biological standpoint as well as an epidemiological approach are likely to prove indispensable in the search for causal factors.

Résumé

1. Une étude des données épidémiologiques met en lumière le rapport qui existe entre les formes plus graves des états dépressifs et la fin de l'âge mûr la vieillesse et la feminité.

2. L'expérience acquise grâce aux traitements physiques utilisés en psychiatrie au cours des vingt-cinq dernières années confirme dans l'ensemble l'existence de deux types comparativement distincts d'état dépressif, l'un basé sur une prédisposition spécifique, l'autre sur une vulnérabilité générale vis-à-vis de laquelle les individus ne diffèrent qu'au point de vue du degré. Ces deux groupes diffèrent quant à leur image clinique—son inconstance et ses conséquences aussi bien que par le type de prédisposition—plutôt que par la présence ou l'absence de causes environnantes de la maladie.

3. Le rapport entre les états anxieux et les états dépressifs est discuté avec mention particulière d'un nouveau syndrome qui habituellement se manifeste tout à coup après un malheur ou une grave maladie physique. Ce dérangement est plus fréquent chez les femmes qui auraient tendance à être rigides et dépendantes d'autrui. Le noyau même de la maladie est une dépersonnalisation qui se combine avec une forme caractérisée de phobie anxieuse; cette combinaison se trouve accompagnée de symptômes plus variables de dépression, d'obsession, d'hystérie, d'hypocondrie et parfois de psychose de courte durée. Les symptômes de dépression peuvent être plus évidents particulièrement chez des malades plus âgées—mais un traitement d'électrochoc ne fait habituellement qu'aggraver la maladie. On considère que les faits connus sont à l'encontre du concept d'une seule et unique famille des maladies affectives où les différents types de réactions se fondraient insensiblement les uns dans les autres.

4. Les observations récentes ne confirment pas le concept d'un état dépressif d'un type spécifiquement involutif. Mais des preuves permettraient de suggérer que ceux qui passent par un état dépressif pour la première fois à un âge avancé sont moins prédisposés de naissance aux dépressions nerveuses que ceux dont la maladie s'est révélée quand ils étaient plus jeunes. Dans le premier cas une force exogène est le point de départ le plus fréquent et la dépression se complique souvent de troubles physiques, particulièrement chez les hommes.

5. Le rapport qui existe entre d'infimes altérations de la conscience et certaines formes de réactions dépressives est discuté en se basant particulièrement sur les psychoses 'psychogènes', les états dits 'schizophréniformes', les psychoses des épileptiques et des alcooliques et les symptômes affectifs associés avec les maladies somatiques aiguës.

6. Discussion du rapport qui existe entre les symptômes d'hypocondrie et d'obsession et les états dépressifs. Plus les symptômes précédents seront prononcés en

relation avec l'état dépressif, plus le cours de la maladie et la réaction au traitement seront éloignés de ceux de la dépression endogène. Il est suggéré que l'hypocondrie existe en tant que telle aussi bien qu'en tant de symptôme d'un état dépressif. Description de quelques formes cliniques de cette maladie.

7. Les états de dépression sont parmi les plus communs des maux humains. L'incidence morbide des seuls cas endogènes est d'environ 1-2%, ce qui implique une plus grande fréquence que pour toute autre maladie provoquée par un mécanisme génétique spécifique. L'auteur met ces faits en relation avec la psychopathologie et avec la signification biologique des états dépressifs.

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Discussion

ROBERT O. JONES*

Dr. Roth's paper presents a review of some of the problems in the classification of depressive states. He also has included an account of several astute clinical observations, with much original material of the sort that we, on this side of the water, have come to expect from the United Kingdom. Unlike the other discussants, I have had Dr. Roth's paper long enough to go over it, and cannot blame my difficulty in providing stimulating discussion on lack of time; but I have found difficulty because of the similarity between his views and my own. Perhaps it might be said that the same difficulty has marked this conference to date — either we are less aggressive than I believe most psychiatrists are, or we all have a high degree of similarity in our beliefs. It would seem to me that we agree pretty well about what we know and still more about what we don't know and that most of us would agree that it has become obvious that the area which we don't know is by all odds the greatest.

That there is great confusion in the classification of depressive states has been attested to today. Every teacher of psychiatry has known how unsatisfactory the present classification is, especially when he attempts to apply it to his daily work under the critical eye of his students. After twenty years of psychiatric practice in a relatively small and stable community of Scotch, Calvinistic background, I feel that the situation is becoming worse. Such a population produces many depressions, and in the last year or so I have been seeing patients whom I saw fifteen years ago with typical involutional melancholia. These patients are now relapsing, which involutional melancholias of course should not do. Worse still, some of them are presenting with depressive reactions, clearly of the manic depressive type on this occasion, and have had hypomanic episodes in the course of their recovery. Such experiences have convinced me that the distinction between involutional depressions and manic depressive depressions cannot be maintained.

It also seems to me that the depressions in younger people that we see today don't fit diagnostic pigeon-holes as well as they formerly did. I think that the clinical picture of depressions is changing and that the classification gets less satisfactory all the time. With this change, more patients are atypical and respond to therapy atypically or not at all. This change makes it very difficult to compare statistics collected in 1940 with those of 1959, and is an example of the difficulty in applying the epidemiological methods, which Dr. Roth rightly states are valuable.

Another difficulty with such methods is the ease with which they are influenced by local customs of therapy, care, etc. Dr. Roth speculated on the incidence of depressive reaction in the aged in Great Britain and in North America, using figures collected from state mental hospitals. He states that this diagnosis is rarely found in North American figures. I am sure that this is because almost all depressed patients in Canada are treated in general hospitals or in out-patient clinics. Thus they rarely get admitted to mental hospitals and mental hospital statistics in this area are completely unreliable. After all, one is dealing here with the bread and butter of people in private psychiatry. Let me assure Dr. Roth that we who work in this general hospital and out-patient setting see many depressive reactions in the aged. Let me also underline his remarks concerning the effectiveness of therapy in this aging group. Active, aggressive therapy in depressive states in elderly people may not only add much happiness to their years, but may add many years to their lives. Certainly there are few therapeutic experiences in modern psychiatry that can rival this situation in terms of personal satisfaction.

May I conclude by again thanking Dr. Roth for this very fine paper and only complaining that it leaves so little area of disagreement.

General discussion from the floor (summarized)

A speaker from the floor questioned the value of classifying endogenous and non-neurotic depressions as distinct phenomena. He stated that last year's symposium in Paris concluded that there is a continuum and not a distinct group of entities. He felt that different treatments should be applied to depressions of different severity in the same sense that aspirin or morphine might be appropriate to headaches of different severity. Finally, he questioned whether Dr. Roth's category of catastrophic

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reactions was indeed related to depression rather than to the regression from a depressive state to a schizophrenic position.

In replying to the discussants, Dr. Roth stated that classification is not an end in itself but a necessary prerequisite for arriving at causes. Before mental diseases were sorted, it was the custom in Great Britain to assign patients to wards on the basis of age. The result was that many old people were condemned to permanent incarceration who might otherwise have recovered with physical treatment. The term 'phenomenology' is used in two senses: first, in the way it has been used by Jaspers, and secondly to refer to descriptive data about clinical phenomena. Dr. Roth chooses the description of clinical entity rather than of the inner life of the patient, in the belief that this choice brings one closer to the problem of etiological factors. The history of medicine and of science in general shows that greatest success comes through efforts to elicit not what is unique but what particular phenomena are held in common by groups of cases. He questioned the validity of the data from which the Paris symposium concluded that depressive phenomena form a continuum. Assertions have no value whatsoever unless they are backed by an attempt to classify cases into groups on the basis of stated criteria of diagnosis. There is a need for more studies of the sort that were made by Lewis in 1935, which have hardly been equalled for their thoroughness, care and detail, but which were made before the era of physical treatment. Regarding the necessity for classification if the psychodynamic patterns in all depressions are the same, Dr. Roth stated that psychodynamic patterns are presumably the same whether the depression is due to a spirochaete, to a cerebral tumour, or to cerebral arteriosclerosis. In this sense, pyschodynamic factors are rather low down in the hierarchy of causes, even in the case of endogenous depression. While everything in the universe may be causally related, the problem in science is to find factors which have a more specific relation one with the other than with things in general. Regarding the catastrophic reactions presented in the paper, the patients seemed gloomy, sad, agitated and frequently self-accusatory, and therefore presented very frequently as depressions. Seven out of ten cases which came from other clinics had had ECT, almost invariably with a dire consequence and a lasting terror of the treatment.

INDICATIONS FOR ELECTRO-SHOCK, TOFRĀNIL AND PSYCHOTHERAPY IN THE TREATMENT OF DEPRESSIONS*

HANS HOFF**

When we speak of a new kind of treatment in a particular field of psychiatry we must first clarify what it is we are treating. The term "depression" seems to me too general. Much of the confusion as to the value of different forms of therapy in depressive states could be avoided if the terms used to describe these various syndromes were more clearly defined. Depression itself is merely a symptom which may arise in a variety of conditions.

Three forms of depression must be carefully distinguished. The first, reactive or exogenous depression, is caused and maintained by unfavourable external conditions of life. It is obvious that someone who experiences a major tragedy in the family or a business setback will be affected by it, but this is a perfectly normal reaction and not a disease. The second form of depression, neurotic depression, occurs during the course of a neurosis and is due to the secondary reaction of the personality after failing to deal with the primary neurotic symptoms. The patient is aware of the impoverishment of his personality arising out of the struggle with the irrational unconscious conflict and of the subsequent regression, and reacts to this with a depression. The third form of depression, endogenous depression or melancholia, is the expression of a genuine, possibly organic disease belonging to the group of manic-depressive psychoses. In Vienna we adhere to the classical symptomatology of endogenous depression, and before making a diagnosis we require to see the following symptoms:

1. Primary despondent mood.
2. Inhibition.
3. Anxiety.
4. Absolute pessimism.
5. Self-reproach.
6. Tendency to suicide.
7. Remission in the evening.
8. Poor insight into the condition.
9. Feelings of inferiority.
10. Physical symptoms (dryness of the mouth, constipation, wasting).

The endogenous depressive phase as part of manic-depressive psychosis may occur in various forms. There may be a single phase during the whole life of the patient, but this is rather rare and accurate history-taking will in all probability reveal the existence of other sub-clinical phases which were not severe enough to require medical treatment. Another form of endogenous depression is recurrent or periodic melancholia, i.e. several such phases during a life-time. These phases may resemble one another with almost photographic accuracy but they can also differ widely. The free intervals between phases may vary in length considerably, from a matter of a few days to several years. Where the depressive phases recur with almost photographic accuracy we should possess a valuable method of comparing various methods of treatment. Unfortunately this similarity of the phases usually concerns the symptomatology and not the length of the phase. Finally there is the true manic-depressive type of phase, where both manic and depressive phases occur in one and the same patient. It provides a difficult therapeutic problem, especially when one phase rapidly passes over into the other.

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*Translation.

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Although severe manic phases, here as elsewhere in the world, have become less common, we find mild manic fluctuations in a large number of patients who have gone through phases of depression. The hypomanic swing at the end of the depressive phase is characteristic.

We are of the opinion that the general body of symptoms, the course of the disease and the study of heredity justify us in retaining the concept of manic-depressive psychosis. We believe that endogenous depression, just like any other psychic disease, is due to many factors. We think heredity is a more important factor in the origin of the disease than it is in schizophrenia. We agree with Kretschmer that a certain constitutional form tends to predispose towards depressive swings, but we consider the constitutional factor less marked than in the case of schizophrenia. A certain psychodynamic development also appears to be necessary and we think that here the first disturbances already occur in the second oral phase. The family situation is also often characteristic. We know the mother of the manic-depressive patient, just as we know the mother of the schizophrenic. She, too, is a domineering mother, less anxious but much more exact and pedantic and subject to greater fluctuations in mood than the mother of the schizophrenic.

Finally, in the production of depression some precipitating factor is necessary which is usually much more clear than that which precipitates a schizophrenic episode. This precipitating factor has to strike in a critical phase of the patient's life. It is clear therefore why the commencement of an endogenous depression often coincides with a critical period of life such as puberty, completion of social development (between the ages of 20 and 24), involution and old age.

We must stress the fact, however, that with repeated attacks the precipitating factor recedes more and more into the background. This is probably due to a much greater participation of the vegetative nervous system, which evokes the same reactions in a preformative manner.

In assessing endogenous depression we must not ignore the situation of the patient nor the influence of the depression on his surroundings. We know that the melancholic patient irritates and depresses all around him and is then further depressed by their reaction to him.

We have mentioned all the multiple factors which play a part in the origin of endogenous depression, and they are certainly important. But we should not stress any one factor too much and lose sight of the whole since this would result in a confused diagnosis.

Some forms of depression may be difficult to classify into one of these groups, and only the further course of the condition clarifies the diagnosis. Moreover, all manner of combinations are possible, e.g. a reactive depression which passes over into a true endogenous depression or one in which both a neurotic and endogenous component are present. However, in the great majority of cases classification under one or other of the groups mentioned is possible and is a decisive factor both for prognosis and therapy.

What is characteristic of endogenous depression? We believe that healthy persons under certain circumstances may be just as sad, anxious and pessimistic as the endogenous depressive patient. But two phenomena are characteristic of the latter. One is the persistence of the depressed mood, the fixity with which it is maintained, visible in the emotional and vegetative reactions as well as in the movements. The other phenomenon, only seemingly an antithesis of the first, is the possibility of a sudden switch in a matter of seconds to the opposite mood, a manic state. This sudden switch, which is never quite so dramatic in normal persons and can be seen for a short time in almost all true endogenous depressions, involves all levels of the personality and is particularly manifest in the vegetative

sphere (Selbach's "Kippreaktion"). These two phenomena help to confirm the diagnosis of endogenous depression.

This differentiation among the various forms of depression provides us with indications as regards therapy.

Exogenous depression due to obvious external stress can only be helped by reducing this stress or by just being humanly helpful. The doctor can do more here by friendly assistance than by any medical treatment. Indeed it is a moot point whether drugs can do such patients any good since they get the impression that they are ill, whereas in reality they are merely displaying a normal reaction. Any improvement in an exogenous depression brought about by drugs is probably purely suggestive, and can be attributed to the personal relationship between doctor and patient.

In neurotic depression treatment must be aimed of course at the basic symptoms of neurosis. Psychotherapy is here the treatment of choice. If the secondary depression renders the patient unresponsive to psychotherapy then in some cases drugs may be helpful. The patient must be clearly told, however, that the drug is only for the secondary depression and is purely supportive treatment. There is one danger here, that side effects resulting from the drug may be employed as conversion symptoms by the patient. This is important with drugs such as the neuroleptics with their pronounced vegetative side effects. We are of the opinion that in neurotic depression drugs should only be used with the utmost circumspection and only when the psychotherapeutic contact is good.

In endogenous depression the situation is quite different. We have seen that endogenous depression is at least in part due to organic conditions or is organically fixated. It also responds to organic therapy. We are not yet in a position to carry out a causal therapy because we know nothing of the nature or localization of the disturbance. We can therefore attempt by symptomatic treatment to shorten the phases of the disease or at least mitigate the symptoms.

Twenty years ago, thanks to the discovery of Cerletti and Bini, electroshock therapy (ECT) was introduced into the treatment of depression. To avoid misunderstandings we must first say a few words about the technique we employ today and the relative risks involved. We always use muscle-relaxants in conjunction with electroshock, and for some considerable time we have been employing succinylcholine chloride, the use of which in ECT was first described in Vienna. We either use small doses (8-10 mg) to prevent bone fractures, which we call mitigated shock, or we use rather high doses (60-100 mg) combined with intravenous anaesthesia and artificial respiration, which we call fully mitigated shock. We employ fully mitigated shock where otherwise there would be medical or surgical contraindications for the use of ECT. Fully mitigated shock, which can be carried out by a doctor and one nurse exactly like normal ECT, should only be performed by a doctor fully trained in anaesthetics and with considerable experience of ECT technique. Almost all accidents which occur during shock treatment are due to some technical error.

We recognize no medical or surgical *contraindication* for ECT apart from recent cardiac infarction. The dangers of ECT, so often stressed, seem to us extremely slight, in fact less than those of almost any drug treatment in psychiatry. In the past five years, out of a total of about 15,000 electroshocks, of which 2000 were fully mitigated, we had not only no death but no complications at all. We never had to interrupt shock treatment because of complications.

How does ECT act in endogenous depression? We believe that electroshock destroys the tendency of endogenous depression to become fixated, and does this at all levels of the personality. The individual shock momentarily changes the activity of all centres in the brain and the normal metabolism of the cells has to be

slowly re-established. In the vegetative system a maximum stress occurs, with all the features of the stress phenomenon. The vegetative system only gradually swings back into the normal state and the process may take several days. The end effect is that the sympathicotonic component of the vegetative system is reinforced, which benefits the more vagotonic depression. The whole content of the psyche is obliterated and patients wake confused out of the shock, remain amnesic for hours and have to collect their psychic content again laboriously. This process is of relatively short duration after the first shock, but after repeated shocks takes longer and longer.

The effectiveness of ECT depends to a large extent on subsequent shocks being given *at the correct moment.* The next shock must be given before the depression has again become fixed at all levels. This produces a summation of effect. ECT is therefore only effective when applied in a series at short intervals. At the commencement of treatment 48 hours would seem to be the maximum permissible interval. After several shocks, when the amnesic interval lasts longer, the time between shocks can be increased to three days and in older patients possibly to four days, but not longer. The amnesia is part of the action of ECT. All attempts to lessen it or avoid it impair the effectiveness of the treatment. Amnesia occurs in fully mitigated shock just as much as in unmitigated shock. Bad results with ECT are usually due to an insufficient number of shocks or to irregularity in the treatment. Excessive prolongation of ECT is also not right. Patients can get used to ECT just as they do to drugs. There are patients who can talk intelligibly and coherently five minutes after an electroshock, particularly if they have received a great number of shocks at irregular intervals.

If a series of six up to a maximum of twelve electroshocks proves unsuccessful, they must be stopped and another series given only after an interval of some weeks to several months (this of course only applies to endogenous depression, not to schizophrenia). Successes with ECT in typical endogenous depression, and indeed in all forms of depression, attain the very high proportion of over 80%. The occasional failure of ECT leads us to question the diagnosis, when we nearly always find encephalographic evidence of cerebral atrophy. ECT is also less effective where there is a big neurotic component in the depression, and also when external difficulties persist and give it an exogenous basis.

At the end of every successful shock treatment we try to follow up with psychotherapy of course, in order to treat those factors arising in the patient's own psyche which predispose towards a relapse, but here we meet with difficulties. Once cured, the patient with endogenous depression feels perfectly well and wants to hear no more of his illness. His attitude is quite different from that of the schizophrenic. The schizophrenic may show some insight into his condition and he often makes an attempt to understand the morbid phenomena. He is therefore particularly amenable at this stage to psychotherapy. The patient with endogenous depression is different, has no understanding of his symptoms and cannot see why he should continue to be treated. The attitude is different when there is a neurotic element in the depression and it is then easier to follow up ECT with psychotherapy.

We have not therefore had very satisfactory results with psychotherapy in endogenous depression, but we are still looking for a solution.

The shock treatment of endogenous depression is very successful and is certainly one of the most successful forms of therapy in the whole field of medicine. In spite of this, attempts are always being made to force its abandonment. This attitude is understandable on the part of patients and relatives. There is a common fear of the term "shock" and of an electric current, and of a permanent damage to the personality. Many patients think their minds can be permanently affected or memory impaired. Many patients find the idea of going to hospital for shock

treatment unpleasant. ECT for out-patients is fraught with difficulties and we think it can only be done exceptionally and with special precautions. This fear of ECT and of hospitalization results in many patients with endogenous depression not going to the doctor at all, and then being committed forcibly to hospital in a much later stage of the illness or following a suicide attempt. This state of affairs has improved somewhat in recent years but is still unsatisfactory.

Any treatment, therefore, which could replace ECT and did not have these disadvantages would be welcome. In this respect the new drug Tofrānil* seemed to offer possibilities. I would now like to report on our experience with this drug and also draw some conclusions from it of use for the further therapy of depression.

I will not take up your time with a repetition of the chemical and pharmacological properties but will merely point out that the similarities of the nucleus with that of phenothiazine and of the side chain with that of chlorpromazine suggest a similar action.

This resemblance is, however, only partial. Our doctors, by trials on themselves and by exact questioning of patients, have attempted to establish in the first place the action of a single large dose (50-100 mg) of Tofrānil on the psyche. There was general agreement that Tofrānil, after a latent period of about half an hour, causes a sense of tiredness and of distance, similar to that produced by phenothiazines but much less. A second component was a certain inner restlessness, or as one of my doctors put it, an "inner quivering." The total effect was like the feeling one has when one is over-tired and unable to get to sleep. It is interesting that none of the healthy test persons found any euphoric or stimulating effect. On the other hand, many patients with endogenous depression state that they feel a distinct improvement in mood and capacity to work.

When used for a short course of treatment, Tofrānil acts on the basic depressive mood and inhibition. A general activation takes place, the patients get up earlier in the morning, are prepared to work, their movements become more brisk and the facial expression loses the tense rigidity of the depressive. Patients acquire a sense of distance from their depressive symptoms, similar to that which neuroleptics provide in the case of schizophrenic symptoms. There is no direct effect on a number of depressive symptoms such as hypochondriacal ideas, agitation or anxiety; on the contrary agitation is often reinforced. Nor are schizophrenic symptoms, particularly delusions and hallucinations, affected.

For out-patients we chose a dosage of 150-250 mg per day and we always tried to give the highest dose which could be tolerated without causing side effects or impairing the capacity to work.

In hospital we usually commenced with injections, increasing in the course of 3-4 days to a total amount of 150-200 mg, then gradually replacing injections by double the amount by mouth. We usually reached in this way a dose of 300 mg per day which was gradually reduced after the symptoms of depression had disappeared, leaving a maintenance dose of about 150 mg per day. We often began with tablets from the outset and increased the dose within a matter of days from 150 to 300 mg per day. Results did not seem to depend absolutely on the size of the dose. We often noticed that if a dose of moderate size was of no avail, increasing it did not necessarily bring success.

The drug was well tolerated by those patients who displayed no untoward side effects. Initial tiredness soon disappeared, so that patients could work while undergoing treatment. There is little effect on the circulation, although occasionally mild tachycardia was seen. We have seen no case of collapse, but since several have been

*Trade Mark.

described in the literature, we were cautious at the commencement of treatment and prescribed rest in bed.

Sleep is improved in about two-thirds of cases and rendered less good in one-third. This variable reaction is explained by the two component actions which we discussed earlier. Where sleep is poor, Tofrānil may be combined with hypnotics or possibly with chlorpromazine. We should add that Tofrānil can be combined with any other drug and also with electroshock.

We have treated a total of 120 patients with Tofrānil in the last 8 months. In 31 of them, that is in roughly one-quarter of the cases, we observed untoward side effects or complications. In 12 cases therapy had to be discontinued for this reason.

Table 1 summarizes the side effects and complications. Some side effects such as dryness of the mouth and increased secretion of sweat are very common, but are not found to be particularly distressing. A feeling of weight in the abdomen, nausea and constipation are often mentioned but should be treated with reserve in a condition like depression. Giddiness and tachycardia depend on the dose and can be ameliorated by reducing it.

TABLE 1
Side effects and complications due to Tofrānil
(in 120 cases)

		Number of side effects	No. of cases in which treatment was discontinued
Dryness of the mouth		(in over 50% of cases)	
Hyperhidrosis		(in over 50% of cases)	
Gastrointestinal symptoms		9	1
Giddiness, tachycardia		15	2
Allergic exanthem	Total No.	5	3
Tremor	of cases:	8	4
Choreiform twitching	31	2	2
Disturbance of accommodation		3	
Icterus*		1	

*Probably not a side effect of the drug.

In five cases we saw a transient exanthem which disappeared again two days after interrupting treatment and in two cases did not reappear after recommencing Tofrānil. The exanthem was not accompanied by any other allergic phenomena. The very fine tremor observed in 8 cases was interesting. It was quite different from the coarse parkinsonian-like tremor associated with phenothiazine or reserpine. Two patients treated for a relatively long time with rather high doses showed first an intensification of the tremor and then pronounced choreiform twitchings. We examined these cases clinically and electromyographically in detail and believe there were lesions of the ascending fibres in the reticular formation of the brain stem, but we cannot go into this in greater detail in this paper. The twitchings disappeared two or three days after discontinuing Tofrānil. An unpleasant effect was total retention of urine in two cases, necessitating indwelling catheters. It persisted in one case one week after stopping Tofrānil and in the other three weeks. We are not sure, however, that in the second case, a woman patient, the disturbance did not become psychically fixated. This retention of urine, which was accompanied by a peculiar frontal picture and crossing of the legs when walking, reminded us of the cases of centrally originating retention of urine following lesions of the basal parts of the caudate nucleus described by Harburg. It may provide a hint as to one of the sites at which Tofrānil acts. Interference with accommodation, seen in three cases, was very similar to that caused by phenothiazines. One case of icterus oc-

TABLE 2
Summary of patients treated with Tofrānil
Total Number: 83 (40 men, 43 women; 62 in-patients, 21 out-patients)

Diagnosis	Number of cases	Results		
		−	+	++
Endogenous depression	50	17	22	11
Cyclic depression	4	2	2	
Neurotic, reactive and psychopathic depression	15	12	3	
Depression in schizophrenia	8	6	2	
Alcoholic depression	3	3		
Cerebral atrophy	3	3		
Totals	83	43	29	11

curred during treatment, but since it showed all the signs of an infectious hepatitis it probably had nothing to do with Tofrānil.

Tofrānil is thus seen to cause relatively frequent side effects but these are in general not particularly dangerous. Severe permanent damage or death did not occur during our treatment.

And now a word about our results with Tofrānil. Out of our 120 cases we have chosen 83 for evaluation. In the other cases treatment had to be discontinued either because of side effects or for other reasons. The cases are classified according to diagnosis in Table 2. A glance at this table shows that real remissions were only obtained in true endogenous depression. In all other conditions only the concomitant depressive symptoms were improved, while the underlying disease was unaffected.

In Table 3 we have summarized our 50 cases of endogenous depression. The four columns show the various grades of improvement. Column 1 contains the completely negative results, cases which did not respond to treatment at all. Column 2 gives the cases which responded well initially but then relapsed so that Tofrānil no longer had any effect. Column 3 contains the majority of cases, those responding markedly to Tofrānil with improvement both in the depressive mood and in the inhibition, but without full remission. We were able to discharge some of them from hospital but they were not fully capable of work. As soon as Tofrānil was discontinued the depression got worse and the drug had to be given again. In these cases there is only symptomatic improvement, the condition becoming more tolerable for the patient while waiting for the depressive phase to pass spontaneously. Interestingly enough, there were four patients in this group with chronic endogenous depression who had responded to no treatment at all and even with electroshock showed only transient improvement. They did not remit fully, but they felt much better than they had for years.

Column 4 contains the complete remissions. They usually occurred relatively quickly between the 3rd and 14th day. Very slow gradual improvement is usually followed by a less favourable end-result than a rapid change in mood. In four cases we saw a subsequent typical hypomanic swing. Remission was maintained even

TABLE 3
Endogenous depression treated with Tofrānil

Type	Number	−	+−	+	++
Mainly inhibited	35	4	3	19	9
Other symptoms in the foreground	11	4	2	3	2
Senile	4	4			
Totals	50	12	5	22	11

after discontinuing Tofrānil. Detailed study of the case histories of these patients, some of whom we knew from previous phases, convinced us that the remissions were not just spontaneous or accidental but a genuine effect of the drug.

The table shows that patients who are sad, apathetic and inhibited respond better than agitated or hypochondriac ones. In four senile depressions there was no success. We are aware that this figure is not significant, but in general it seems to us that with increasing age the efficacy of the drug diminishes and the side effects increase. We believe the drug should not be employed in arteriosclerosis and cerebral atrophy because the effect is too small to warrant the risk of complications.

The best indications for Tofrānil are therefore the more inhibited forms of genuine endogenous depression. In this group the effect is better the less severe the depression. When the inhibition is very severe (substupor or stupor) Tofrānil has usually no effect. In this selected group of endogenous depressions, we had in about one-quarter full remissions and only in one-fifth complete failure. These figures agree well with those of other authors. One can thus conclude that about one-quarter of the patients will show complete remission, about one-half will be improved and another quarter will not respond. Taking complete remissions and improvements together, 75% will respond to treatment.

Now what of the mode of action of Tofrānil? We must admit that with this drug too, practice is in advance of theory and that we possess only the vaguest of notions about its mechanism of action and site of action. We believe that in analogy to phenothiazine there is an effect on the ascending fibres of the reticular formation. We would like to mention the three functions of the tectoreticular formation: the motor function guaranteeing upright posture, the vegetative function coordinating a number of the most important vegetative centres, and the function which causes the brain to react sensorially and emotionally to external stimuli. We know that all these functions are disturbed in endogenous depression, but we also know that in man part of the function of the reticular formation, especially as regards dealing with emotional contents, has been taken over by the thalamus, and we believe that Tofrānil acts on the thalamus.

Since Tofrānil has been found to exert a specific effect on the depressive mood and inhibition we may hope that better knowledge regarding the site of action of this drug will lead to new insight into the mechanism of depression.

Before comparing the effect of Tofrānil and electroshock we should perhaps say a few words about another drug which in recent years has proved valuable in a number of depressive states. We refer to iproniazid, with which we have not had much experience, but sufficient to form an idea of its effect when considered in conjunction with the literature on the subject. The action of iproniazid seems fundamentally different from that of Tofrānil. Iproniazid seems to have no direct effect on the depression but to be a genuine euphoric. It improves the mood not merely in depressive patients but in normal persons too. A consequence of this is that iproniazid seems least successful in true endogenous depression but has some value in depression with a neurotic basis. But we must once more warn against the misuse of drugs with a euphoric effect in neurotic depression. Iproniazid also possesses very unpleasant side effects and in some cases leads to severe jaundice which may terminate fatally. We do not yet know whether its effect justifies its use on a wider scale. However, like Tofrānil, iproniazid might provide valuable insight into the mechanism of psychic disturbances. Studies to date on the inhibition of monamine oxidase and the resulting effect on serotonin and noradrenaline metabolism are very promising.

Finally we would like to compare the effects of Tofrānil and electroshock (ECT). These may be summarized as follows:

1. First the indications: ECT has many more indications than Tofrānil, and just those cases which are indications for Tofrānil react best to ECT. It is therefore not possible to work out a differential indication, i.e. in one group ECT and in another Tofrānil.
2. The number of remissions is three times higher with ECT than with Tofrānil when only full remissions are taken into consideration.
3. Time is an important factor in hospital. We lose a lot of time with unsuccessful Tofrānil treatment, since we then have to give ECT anyway.
4. The quality of the remission obtained with Tofrānil seems to be just as good as that with ECT for any single phase. Nowhere of course has the follow-up time been sufficiently long to say much about relapse. This point seems of some significance because patients who remit with Tofrānil have the advantage of suffering no transient loss of memory.
5. As regards the risks, Tofrānil offers more risk than ECT since side effects and complications are much more frequent than with ECT.

Tofrānil can be employed in combination with ECT either simultaneously or subsequently. Simultaneous combination has not proved of value to us since remissions were neither more rapid nor better than with ECT alone. Furthermore, after unsuccessful Tofrānil treatment we were not able subsequently to reduce the number of electroshocks. On the other hand Tofrānil proved very valuable for the after-treatment of depression following ECT. Sometimes, particularly after insufficient shock treatment, there remained residual fluctuations in mood or an irritable dysphoric mood but these symptoms responded excellently to Tofrānil in 8 cases.

Now what of the further indications for Tofrānil? These may be summarized as follows:

Out-patients: 1. All cases of endogenous depression not endangered by risk of suicide.
2. Mood fluctuations following treatment with electroshock.

In-patients: 1. Endogenous depression, mainly inhibited. Trial treatment for 8-14 days.
2. No success with chronic depression.

The last three indications in this table follow automatically from what has already been said. In hospital and with the right indication we would first make a short trial with Tofrānil and then relatively soon, if this fails, change over to the more promising ECT. Tofrānil may bring improvement in cases which responded to no other treatment. We have already discussed after-treatment following ECT.

Let us turn finally to the important question of the ambulant treatment of endogenous depression. This is a dangerous malady with a mortality, if one excludes that of senile dementia, six times greater than that of all other psychic illnesses put together. This is due to the high proportion of suicides. We know that there is no case of endogenous depression which at one time or another is not liable to the risk of suicide and that the danger is greater when the depression improves because of the disappearance of inhibitions. The doctor who treats an endogenous depression outside hospital thus carries full responsibility for the life of his patient. Every successful suicide of such a patient must be looked upon as an error of judgment on the part of the doctor.

Here I would like to express the hope that all doctors be aware of the seriousness of this risk, so that the use of the new drug Tofrānil, which certainly represents a valuable addition to therapy, may not lead to an increase in the number of suicides in endogenous depression.

For us in Vienna the challenge is not so much the interruption of the depressive phase as the prevention of a relapse. In this respect Tofrānil presents us not only with a problem but with a hope for the future.

Résumé

L'auteur décrit les formes principales de dépression: psychoréactive ou exogène, due à des circonstances extérieures défavorables; dépression névrotique, apparaissant au cours d'une névrose, et provoquée par la réaction de la personnalité; dépression endogène proprement dite, faisant partie des psychoses maniaques dépressives. La psychothérapie constitue le meilleur traitement des deux premières formes, où les médicaments sont, dans l'ensemble, à déconseiller. Dans le traitement de la dépression endogène, l'électrochoc remporte ses meilleurs succès, mais, vu la prévention générale qui s'attache à tous les traitements par choc, une thérapeutique de remplacement serait la bienvenue. Le Tofrānil semble offrir cette possibilité.

L'auteur décrit l'action du Tofrānil et en discute les dosages. Un quart environ des 120 patients traités ont présenté des effets secondaires désagréables qui, 12 fois, ont nécessité une interruption de la médication. Ces effets — en général peu graves — sont examinés. Dans quelques cas, la localisation possible de lésions dans le système nerveux central est discutée en détail, en ce sens qu'elles permettent de se faire une idée du point d'action du Tofrānil.

Les malades inhibés ou apathiques réagissent mieux au Tofrānil que les agités. D'une manière générale, le médicament agit moins bien chez les personnes âgées, et provoque plus souvent des effets secondaires. Le Tofrānil semble contre-indiqué dans l'artériosclérose et l'atrophie cérébrale, son effet étant trop faible pour contrebalancer les risques de complications.

Les formes les plus inhibées des dépressions endogènes vraies constituent les indications les plus favorables pour le Tofrānil. L'effet est d'autant meilleur que la dépression est plus légère. Dans un groupe de 50 patients, l'auteur a eu 25% de rémissions complètes, 50% d'améliorations et seulement 20% d'échecs complets. Rémissions et améliorations constituent le 75% du chiffre total des patients. Ce résultat concorde avec les chiffres indiqués par d'autres auteurs.

Une comparaison est faite entre le Tofrānil et l'électrochoc. Les indications de ce dernier sont plus nombreuses, il amène un nombre de rémissions trois fois plus élevé, et celles-ci surviennent dans un laps de temps plus bref. La qualité des rémissions est aussi bonne par l'une des méthodes que par l'autre. Le Tofrānil provoque davantage d'effets secondaires. Il s'est montré précieux dans le traitement des dépressions résiduelles, après la cure par l'électrochoc.

En milieu hospitalier, et une fois l'indication correctement posée, l'auteur propose de faire d'abord un court essai (8-14 jours) au Tofrānil, et en cas d'échec, de passer à la thérapeutique par le choc. Le Tofrānil peut apporter l'amélioration, là où toutes les autres méthodes ont échoué. En clientèle libre, la prudence est de mise, du fait que la dépression endogène comporte un gros risque de suicide.

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Discussion

A. E. Moll*

Listening to Dr. Hoff's presentation, one cannot but be impressed by his clarity of thinking and orderly exposition of the material dealt with. He found Tofrānil to be most effective in the classical cases

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of endogenous depression, and more particularly in patients in whom the main presenting symptom is inhibition. These findings are consistent with those of other research workers, such as Lehmann (1), Fazio (2), Kuhn (3), and find confirmation in Mann's research (4) on 80 cases treated with Tofrānil during the past year at the Montreal General Hospital.

Azima and Vispo (5), of the Allan Memorial Institute of Psychiatry in Montreal, however, obtained equally as good a response in neurotics as in psychotic depressions; and in my experience 4 cases of obsessive compulsive personality suffering from severe reactive depression benefited from Tofrānil therapy. These patients had such a rigid personality structure that they proved unapproachable to psychotherapy. Prior to Tofrānil, similar cases would have been treated with electroshock therapy because of their obsessive suicidal ruminations. In two of them the improvement after only a few days on Tofrānil was such that psychotherapy became possible. Another patient, a woman of 38, became extremely depressed because of sudden panic attacks of hysterical nature, which made it impossible for her to go to church or to go out in crowds. The symptoms had been present for years — indeed, for over 15 years she had been unable to go shopping by herself, and could only do so when accompanied by a friend. Tofrānil removed the depression, her panic states decreased in intensity and frequency and the patient is now undergoing psychotherapy. This brings up the difficulty and complexity of assessing what has produced the improvement, pharmacotherapy or psychotherapy — or better still, how much is the improvement due to one or the other or to both.

Another difficulty in assessing the results of treatment is the classification of depressions. There are a large number of depressions which do not allow a clear-cut differential diagnosis: for instance, neurotic depressions and endogenous depressions. There are many depressions which are of mixed type, or atypical. Generally speaking, one may state that the precipitating factors of depressions represent either a loss of self-esteem or a loss of supply which, to the patient, would secure or even enhance his self-esteem. There are experiences which, even for a normal person, would imply loss of self-esteem, such as failure, loss of prestige, loss of money, a condition of remorse, or experiences which entail a loss of some external supply, such as disappointment in love or the death of a beloved one. Further, there may be tasks which the patient has to fulfill and which may make him more aware of his inferiority.

Even experiences that for a normal person would mean an increase in self-esteem may precipitate a depression if the achievement produces in the patient the fear of punishment or of further imposition or guilt. A case in hand is that of a 55-year-old successful chartered accountant who, two weeks prior to his admission to hospital for a severe depression, had been nominated to a very important position. His success suddenly and acutely led him to feel overwhelmed by feelings of inadequacy and despondency. He lost all interest in his job, complained of difficulty in concentration, became agitated and anxious, lost 9 lb. in weight in a fortnight, suffered from disturbance of his sleeping pattern, waking up early in the morning and lying awake ruminating about suicide. This patient was placed on Tofrānil up to a maximum of 200 mg per day. There was little change in his depression for the first few days; indeed, his agitation increased, necessitating the addition of chlorpromazine, 25 mg t.i.d. By the fifth day, however, there was noticeable lifting of the depression and two weeks after admission to hospital he was discharged.

Other cases of depression due to decompensation of obsessive compulsive defenses have not responded to Tofrānil.

The borderline between neurotic depressions, with the patient's ambivalent relationship to external objects in his quest for narcissistic supplies, and psychotic depressions where the conflict has become internalized, is not a sharp one. The increased need of narcissistic supplies by the depressed patient leads to the feeling, "nobody loves me," but the latter does not often lead to the feeling "everybody hates me." Indeed, in the classic depressions, the feeling is the opposite: namely, that they are not hated enough, the characteristic position being not so much "everybody hates me" as "I hate myself." Delusions of being hated by everybody occur more frequently in cases of depressions with paranoid traits. Tofrānil appears to be much less effective in the latter cases.

Dr. Hoff reported three cases of alcoholic depressions treated with Tofrānil with poor results. I have treated one case of alcoholic depression with equally poor results: namely, a business man of 58 who, off and on for the past 20 years, has been subject to alcoholic sprees of 7-10 days duration, with an average daily consumption of alcohol of 40 oz. These alcoholic sprees coincided with depressive phases, his normal mood being mildly hypomanic. Time does not allow me to go into the psychodynamics of the case. Suffice it to say that his last alcoholic bout was precipitated by his wife remonstrating at breakfast to his asking for two pieces of toast instead of the usual one, and his daughter chipping in, "you know you never eat two pieces of toast." As a child he always felt that nobody was really interested in him. He stated that his "pet hates" were "apple cores, cigarettes in ashtrays or in coffee cups, Kleenex left around." On his last admission he presented the symptoms of an endogenous depression, and he was treated with Tofrānil — treatment which he soon gave up because of the side effects: namely, sweating, particularly of the face.

As mentioned by Dr. Hoff, perspiration appears to be a frequent complaint by patients on Tofrānil. Statements such as "perspiration pours down my face like water," or "I perspire gallons of water," are quite common. It is rather interesting, when one inquires about the site of perspiration, that the great majority of patients complain of perspiration of the face and not so much of perspiration on the rest of the body, such as axillae, hands and feet. Two of my patients actually denied perspiring in any other part of the body except the face.

Side effects do not always prove to be of nuisance value. Indeed, I can mention one case in which one side effect proved to be beneficial. This was in a female patient of 47 who was subject to phases of depression. Her sister is beset by phobias and is alcoholic. Her brother is a manic depressive of the cyclic type. There is also a history of allergy in the family, her father having asthma and her mother's brother chronic bronchitis. The patient herself is sensitive to drugs such as penicillin, though no specific sensitiv-

ity was elicited by the usual skin tests. When seen by me she was quite depressed, and unable to carry on with her job. She was prescribed Tofrānil and within two weeks not only the depression lifted, but her 'allergy' also vanished. "I'm not sick at all — I'm myself again. I don't understand it because my problems are still there. I am sleeping well. My appetite is good — such a relief to be able to eat. My allergy is cured. My nose used to run all the time, my eyes swell, they would water, and people in the office always thought that I had a cold. They would say 'you can't work like this — go home.' "

R. Mann, in a personal communication, reported similar good results in a female patient with sensitivity to several allergens. This is not surprising since in some patients allergic symptoms are in the nature of depressive equivalents. Dancey, also in a personal communication, reported prompt response to Tofrānil in two cases of chronic and intractable diarrhoea.

Pharmacotherapy is indeed opening new channels of discovery to the research workers in psychiatry.

Tofrānil, if taken in large amounts, that is, well beyond the usually recommended therapeutic doses, can be very toxic. A female patient of 21, suffering from a character disorder and a depressive reaction, attempted suicide by ingesting 100 Tofrānil tablets as follows: at 7:45 p.m. she ingested six 25-mg tablets; between 8:00 and 8:30 p.m. she had tea and toast; at approximately 8:45 p.m. she ingested the rest of the bottle containing 100 tablets. She reported this at 9:15 p.m., at which time she was slightly drowsy but fully conscious. Gastric lavage was done, and when the gastric tube was inserted the patient began to vomit. Inspection of the vomitus revealed no intact tablets. Following the lavage the patient apologized for causing so much trouble, thanked the doctor and walked unaided to her room. At 10 p.m. she became unconscious. The colour was good, the skin was pale, warm and dry, but the mucous membranes were moist. Blood pressure was 90/50 (normal for this patient), pulse 120 per minute, full and bounding. Both arterial and venous pulsations were strikingly visible in the neck, respirations were 32 per minute, deep and stertorous. Patient was stuporous but responded to any stimulation by becoming restless. When her name was called she would open her eyes and stretch her arms, with marked ataxia, but made no sound. She withdrew briskly from any stimulation. Any stimulus, sound, skin stimulation, even the room light, would increase her restlessness and agitation. The pupils were dilated, but responded to light with a brisk but small contraction. Deep tendon reflexes were all markedly hyperactive, but were bilaterally symmetrical. It was difficult to be sure, because of the brisk withdrawal response, but bilateral Babinski responses appeared to be present.

Vital signs were recorded every 15 minutes throughout the night. During the next hour the level of consciousness seemed to decrease and the sensitivity to stimuli to increase. At 11 p.m. while being examined, the patient had a typical tonic-clonic bilateral symmetrical grand mal seizure, lasting between 5-10 seconds. This appeared to be directly related to the skin stimulation during the examination. Respiration was resumed immediately after the cessation of the convulsion. It was shallow for the first few breaths, then deep and regular. The patient was much quieter after the seizure. To prevent further seizures she was given gr. 7½ of sodium amytal intramuscularly. The room was darkened and the patient was kept as quiet as possible. At 12:30 a.m. the blood pressure was 80/50, and pulse was 100. Respiration had fallen to 22 per min. By 1:30 a.m. the blood pressure had risen again to 90/50, and the pulse to 110 per min. Respiration had fallen to 20 per min., and excursions were normal. They remained so from then on. At 2 a.m. she would open her eyes when called by name. At 3.30 a.m. she would move her arms and legs when spoken to, and at 6 a.m. she was awake, complaining that her arms were stiff and painful, and asked for a drink and a cigarette. She was given a drink of juice and she complained of sore throat. She remained drowsy throughout the following day, but was easily roused and well oriented. Slight ataxia of the arms was noted, intermittent choreiform movements of the arms and about the mouth were observed. She was given sodium amytal gr. 1 p.c. t.i.d. Temperature was not recorded during the acute phase of the poisoning but the following day it was noted to be slightly above her normal baseline, reaching a maximum of 99.4°. Thirty-six hours after the ingestion of the Tofrānil the patient appeared to have completely recovered. Her only complaint was a pain and tenderness in both biceps tendons, which may have been related to the seizure. At this time she was questioned as to what she remembered about the event after she took the pills. The last thing the patient remembered clearly was telling the nurse that she had taken the pills. In spite of the fact that she had talked to the doctor after the gastric lavage, her only memory of it was a vague recollection of seeing the tube with a bulb on it. Analysis of the urine specimen revealed the presence of free Tofrānil. In this case it is impossible to say how much of the drug was actually absorbed. It seems safe to assume that it was much larger than the usual therapeutic dose. (This case was reported by Dr. A. G. Catterson, Assistant Resident in the Department of Psychiatry of Montreal General Hospital.)

I have one case to report in which Tofrānil in therapeutic doses showed an alarming change in the haemogram. A male patient of 34 was prescribed Tofrānil up to 200 mg daily, on August 15th. His white count on that day was: 7,500 W.B.C.; 80% neutrophils, 1% eosinophils; 13% lymphocytes, 6% monocytes. On August 27th: 9,750 W.B.C.; 50% neutrophils, 4% eosinophils, 42% lymphocytes, 4% monocytes. On September 3rd: 16,000 W.B.C.; 66% neutrophils, 2% eosinophils, 29% lymphocytes, and 3% monocytes. Unaware of these findings, the patient was kept on Tofrānil, and on September 9th the white blood cells were 42,600; 89% neutrophils, no eosinophils, 6% lymphocytes, and 5% monocytes. This time the changes in the haemogram were reported and Tofrānil medication was promptly discontinued, with the following events: on September 12th, 29,500 W.B.C.; 60% neutrophils, 6% eosinophils, 33% lymphocytes, 1% monocytes. September 16th, 12,350 W.B.C.; 60% neutrophils, 6% eosinophils, 32% lymphocytes, and 2% monocytes. Throughout this time, repeated tests of the alkaline phosphatase proved normal. The patient recovered.

In the past four months we have had 4 cases with leucocytosis and shift to the left with toxic granulations.

Age need not be a contraindication to Tofrānil therapy. A male patient of 76 was admitted to hospital suffering from a depression. He suffered also from diabetes, hepatomegaly of undetermined origin, non-specific colitis, diverticulosis of the colon, and external hemorrhoids. In his regression, like a hungry infant, he was extremely demanding towards the nurses, doctors, residents and patients. The need for narcissistic supplies was so intense that even in an all-giving environment it soon produced rejection and consequently more regression. He was placed on Tofrānil therapy and after two weeks he became somewhat euphoric. Incidentally, in this case, there was also evidence of cerebral organic changes with electroencephalographic findings.

Organic cerebral pathology need not be a contraindication to Tofrānil therapy, as illustrated by a female patient of 66 who, throughout the past 10 years, has required several admissions to hospitals and mental institutions, and several courses of electroshock therapy. Her blood pressure was more or less stabilized at 200/130, with left ventricular hypertrophy. She had been treated for recurrent depression for the past 30 years, and in later years the depressions tumbled over each other with ever-increasing speed. Following are the list of admissions since 1954 — August, 1955; February, 1956; July, 1956; February, 1957; August, 1957; December, 1957; June, 1958. She had to be treated with a course of electroshock therapy on each occasion, her husband refusing to have her committed. In 1953 she had a stroke and again in 1957. She believed in faith healing and on every occasion she refused to be admitted to hospital until she had to be practically carried into the hospital by her husband because of her extremely acute condition. On her last admission on June 26th, 1958, she was prescribed Tofrānil, 50 mg intramuscularly b.i.d. She was totally negativistic and was given five ECT's to make her more manageable and cooperative. Her depression lifted and was replaced by arthritis. She was discharged one month later "recovered". She has been well ever since, her maintenance dosage being 100 mg daily.

From the above one might gather the impression that I am a Tofrānil enthusiast, and indeed I have seen some remarkable "cures," but I am too conservative to be an enthusiast about any form of drug therapy. In the past 10 years enthusiasm has waxed and waned about the discovery of any new drug. In the field of medicine ACTH and cortisone, when first discovered, were supposed to cure all, until one found that they did not remove disease but only suppressed it. Tofrānil appears to do exactly that in the case of endogenous depression, since it is recommended that the drug be used as long as the natural course of the depressive episode is thought to last. If therapy is discontinued prematurely during the active phase of the depression, the symptoms may recur. When chlorpromazine and promazine came on to the market they also were supposed to be cure-alls until, through diligent investigation and experience, it was found what they were good for and what they were not good for. It is my opinion that the same phenomenon will take place in the case of Tofrānil. It is my opinion that over-enthusiasm may actually lead to disappointment which, in turn, may by over-reaction lead to non-usage of the drug, even in cases in which the drug could be most effective. Perhaps, with further research, we will be able to relate the efficacy or lack of efficacy of Tofrānil to the psychopathology of depressions. We must not lose sight of the fact that depressive illnesses, though very common, represent only a fraction of all psychiatric disorders, and psychiatry may lose out from too rosy promises to the public of easy cure of mental illnesses.

I enjoyed listening to Dr. Hoff's presentation. His conservative outlook finds an echo in my thinking.

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General discussion from the floor (summarized)

A discussant from the floor agreed with Dr. Hoff that clarity in classification and terminology is important; first to decide what type of treatment is best, and secondly to move closer to etiological understanding. He agreed that endogenous depressions respond better to Tofrānil than atypical depressions, and asked if Dr. Hoff agreed that iproniazid is more useful than ECT for atypical depressions which do not respond to electric shock or to Tofrānil. Secondly, he asked if Dr. Hoff agreed with his impression that unsuccessful pre-treatment with Tofrānil reduced the number of ECT's necessary for recovery.

A second discussant from the floor stated that the core of the discussion was when to use Tofrānil as opposed to ECT, and asked Dr. Hoff's opinion on this point. He also stated that in England, the vast majority of depressed patients have ECT on an out-patient basis, and that the suicide rate has been very low. One reason for suicide is the threat of going to a mental hospital for treatment.

A third discussant from the floor cited two cases of chronic diarrhea in severe obsessive-compulsive personalities who tended to develop depression as their defenses decompensated. Both patients experienced marked relief, both from diarrhea and depression. One patient developed giant urticaria, but it was impossible to tell whether this was due to the Tofrānil or to a sedative which was given to counteract a feeling of inner trembling.

Dr. Hoff stated in reply to the discussants that there really is no essential difference in the way cases are diagnosed in Europe and in America. There might be a difference of opinion in a particular case, but not in the majority of cases. He felt that he was in an odd position because he and Schilder had once tried to destroy the Kraepelinian nomenclature because of the feeling that psychodynamics and

personal reactions were more important. Now, however, since a treatment has become available, diagnosis is essential. Dr. Hoff agreed that iproniazid has an effect on every kind of depression, while Tofrānil is effective only in endogenous depressions, but felt that a new drug, similar to iproniazid but less dangerous, may soon become available. Endogenous depression has a multi-factor etiology, with hereditary, organic and psychodynamic factors operating in the early part of life, and a precipitating factor at the time of crisis. Melancholia is a psychosomatic disease. Just as a peptic ulcer caused by psychological factors must be treated somatically as well as psychologically, so the same principle applies in melancholia. He was not sure that pre-treatment with Tofrānil reduces the required number of ECT's, but had the impression that it does. However, ECT has fewer side effects.

He agreed that ECT on an out-patient basis is quite acceptable provided one knows the patient and the surroundings in which he lives. He also agreed that sometimes the idea of admission to a mental hospital leads to suicide. However, the self-destructive tendencies associated with the disease are more important. He did not know how to separate those patients who should have Tofrānil from those who should have ECT. Apparently the same group of patients tends to respond to either treatment. In general, he starts Tofrānil treatment if the patient is afraid to have electroshock. This gives time for patient and doctor to know each other, after which the patient will have ECT with less fear. Tofrānil is sometimes successful in patients who do not respond to ECT, and is also useful during the inevitable period of wavering immediately after the patients are discharged from hospital.

CHEMISTRY OF TOFRĀNIL

F. HÄFLIGER*

Exactly 60 years ago Thiele and Holzinger (1) reported the synthesis of iminodibenzyl (10,11-dihydro-5H-dibenz [b,f] azepine) (2), shown in Figure 1. The authors described the characteristics of the new compound (melting point, solubilities, elementary analyses, crystallographic constants, colour reactions),

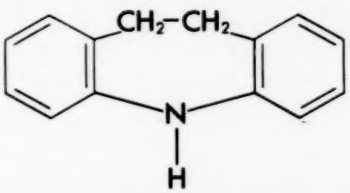

Fig. 1.

its unstable hydrochloride and its nitroso derivative. For nearly 50 years thereafter iminodibenzyl attracted no further attention and was not investigated in any way.

In 1948 we became interested in the compound and included it as a starting material in a broader project involving the synthesis of basically substituted heterocyclic compounds. This project was a continuation of earlier work on antihistaminics, its goal being the synthesis of compounds of potential value as sedatives, analgesics, drugs for treatment of Parkinson's disease, etc. We synthesized a series of derivatives of iminodibenzyl (3), among others those whose structures are shown in Figure 2. In the pharmacologic screening, these compounds showed generally antihistaminic and anticholinergic activity, and some of them in addition showed distinct sedative and analgesic properties (4).

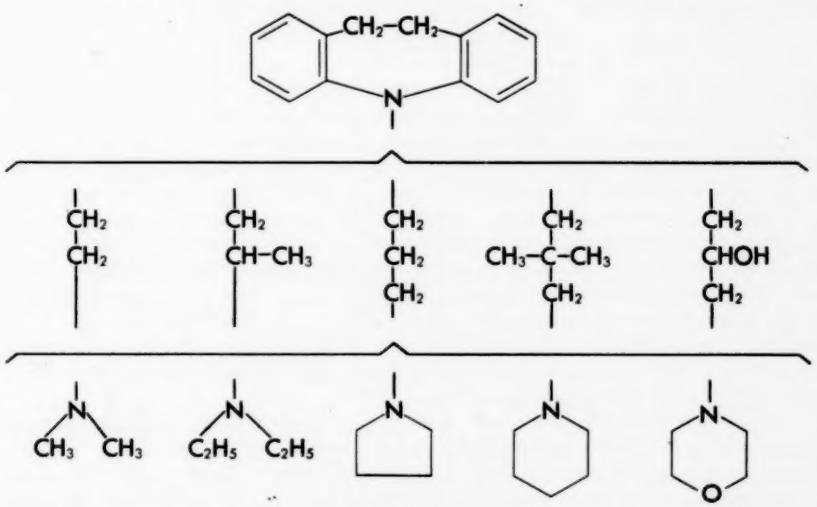

Fig. 2.

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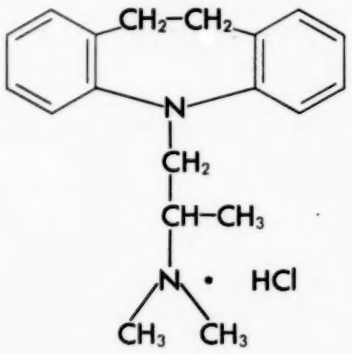
A few selected compounds were then tested in normal human volunteers, and confirmation of the sedative or hypnotic properties, varying in degree between the several compounds, was thereby obtained (5). Based on these results one compound, G 22150, was selected for clinical investigation (Figure 3). The clinical results confirmed the first impressions: G 22150 showed definite hypnotic activity which was, however, not as reliable as that of the barbiturates.



G 22 150

Fig. 3.

The iminodibenzyl derivatives gained for us in importance and interest when it was shown by Delay and Deniker (6) that a phenothiazine derivative, chlorpromazine, was of therapeutic value in the treatment of psychiatric disorders. Like chlorpromazine, some of our iminodibenzyl derivatives had proved to be active in the potentiation of narcosis and "artificial hibernation." Indeed the first iminodibenzyl derivative which was clinically investigated in psychiatry, G 22150, manifested a therapeutic effect comparable to that of chlorpromazine although in a somewhat less potent and less predictable manner. In further tests another compound of the series, G 22355, was found to be of special therapeutic value in the treatment of depressive states (7), a condition in which neither chlorpromazine nor promazine is of value although the latter compound is the exact analog of G 22355 in the phenothiazine series. Chemically designated 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride, G 22355 was introduced in Europe early in 1958 as Tofrānil† after extended clinical trials.

The remarkable differences in the therapeutic effect and certain pharmacologic properties on the one hand, and the structural resemblances between Tofrānil, chlorpromazine, and more especially promazine, on the other, invite one to speculate on the relationship between structure and activity (see Figures 4 and 5). At the present stage of our knowledge such speculation may be considered presumptuous. No harm can be done, however, by some closer scrutiny and consideration of the structures of promazine and Tofrānil.

Within the limitations inherent in all molecular models, it is obvious that the molecules of both promazine and Tofrānil have nearly the same spatial volume and shape and that the side chains and the distance between the two nitrogen atoms are identical. At first glance the only difference between the two structures seems to be the bridge between the two benzene rings, in promazine a sulfur atom, in Tofrānil a $-CH_2-CH_2-$ group. From the chemical point of view this means that in the

†Trade Mark.

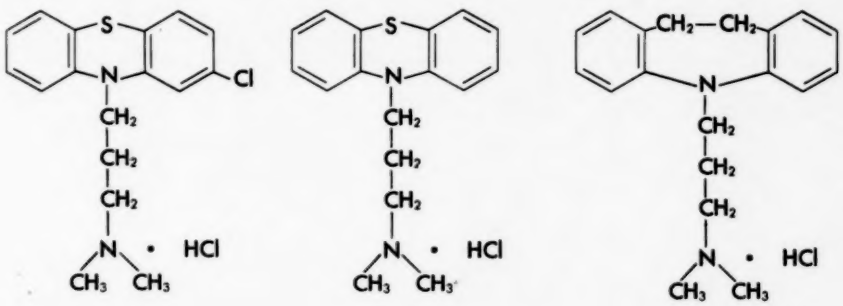


Fig. 4.

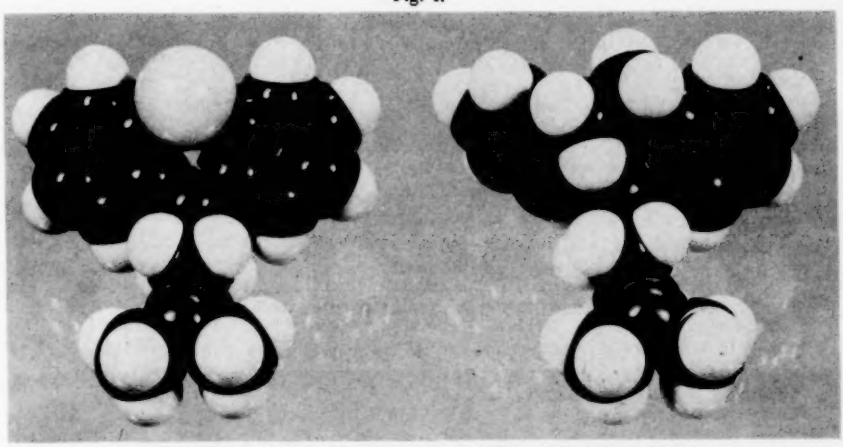


Fig. 5. Molecular models of promazine (left) and Tofrānil (right).

phenothiazine ring system the S-atom enables the conjugation of the benzene rings to extend over the bridge, whereas the -CH_2-CH_2- group in Tofrānil acts as a barrier to conjugation. That this is actually the case is clearly suggested by the U. V. spectra of promazine and Tofrānil, as shown in Figure 6. Whereas Tofrānil shows only one maximum at 250.5 mμ, promazine shows two maxima at 251.5 mμ and 301 mμ as a result of the extended system of conjugation previously mentioned.

Another difference between the two molecules becomes apparent if we focus our attention on the relative positions of the two benzene rings in the respective models (Figure 7). In contrast to promazine, which is a symmetrical molecule, the molecule of Tofrānil is asymmetrical, the two benzene rings being twisted against each other. It is clear that these structural differences between the two molecules must be responsible for the differences in their biologic action. Nothing is known, however, about the mechanisms linking the structures of these compounds with their biologic activity.

A comparison of a few physicochemical properties of promazine and Tofrānil shows no great differences (Table 1). Interesting to note are the very similar pK values, indicating a similar strength of the two bases. The R_f values, in the acid system used, show a slight but distinct difference, whereas they are identical in the neutral system.

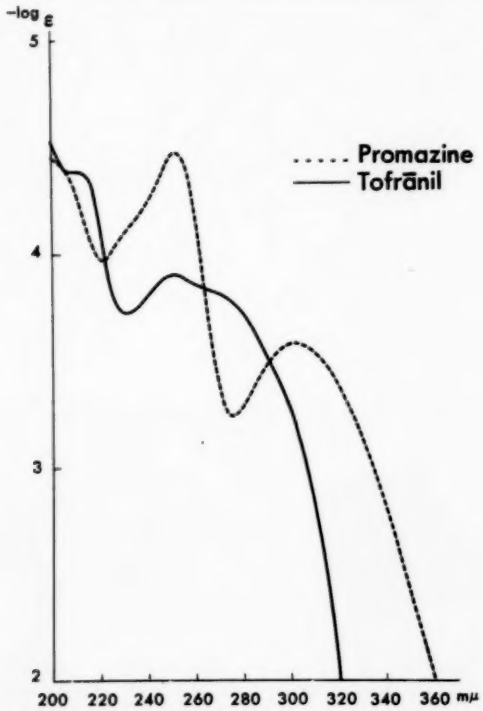


Fig. 6. U. V. Spectra of promazine and Tofrānil (aqueous solutions of the hydrochlorides).

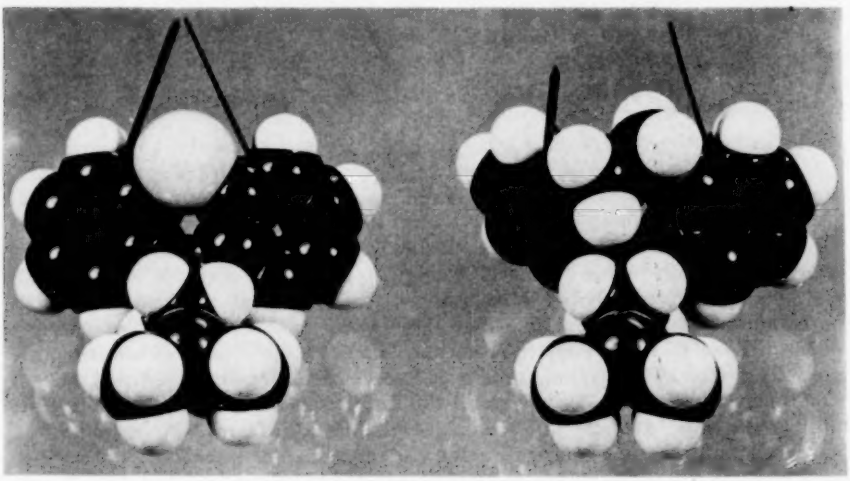


Fig. 7. Molecular models of promazine (left) and Tofrānil (right).
(The pointers lie in the planes of the benzene rings)

Our biochemical studies on resorption, distribution and disposition of Tofrānil have up to now not progressed as far as we would like. We have been limited by the lack of a sufficiently sensitive method of assay. Our efforts in this respect are, how-

TABLE 1
Physicochemical properties of promazine and Tofrānil

	Promazine (hydrochloride)	Tofrānil (hydrochloride)
Empirical formula	$C_{17}H_{21}ClN_2S$	$C_{19}H_{23}ClN_2$
Molecular weight	320.88	316.87
Melting point	182-83° C	173-74° C
pK (in 44% ethanol)	8.5	8.6
R_f value, neutral solvent(1)	0.75	0.75
R_f value, acid solvent(2)	0.75	0.80

1) Butanone:ethanol:water = 70:7.5:40 v/v/v, Whatman No. 3.
2) sec-Butanol:ethanol:acetic acid:water = 15:5:1:5 v/v/v/v, Whatman No. 3.

ever, continuing. With a colorimetric method (limit 0.1 mg%) the following results have been obtained (8): In humans plasma showed measurable concentrations of Tofrānil only for 30 minutes after intravenous or intramuscular injection of 100 mg of the drug, the levels falling below 0.2 mg% a few minutes after injection. The urine of patients treated with Tofrānil contained only about 3% of the administered dose in the form of iminodibenzyl derivatives, among them unchanged Tofrānil, a metabolite of Tofrānil, probably hydroxylated, and another compound which was probably a conjugate of the parent drug.

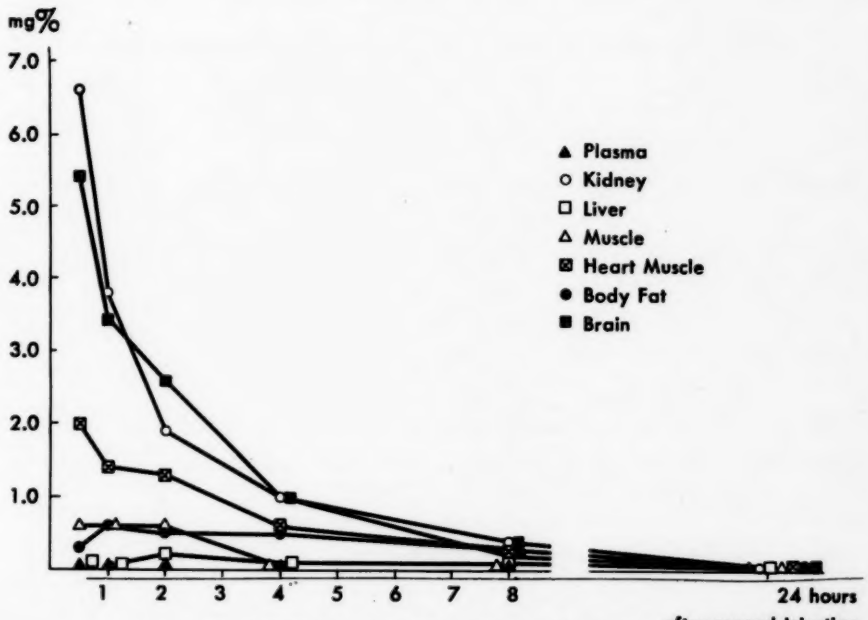


Fig. 8. Tofrānil levels in different tissues of the rabbit.
(Two i.v. injections of 5 mg/kg, 15-minute intervals)

The distribution of Tofrānil in the rabbit is rather interesting (Figure 8). Especially noteworthy are the relatively high levels in the brain as compared with those in the body fat, and those of heart muscle against ordinary muscle. We hope that in the near future more sensitive analytical methods (spectrofluorometric or tracer methods) may help us towards better knowledge of the biochemistry of Tofrānil and thus provide us perhaps with a better understanding of its mode of action.

Résumé

Le Tofrānil, chlorhydrate de 5-(3-diméthylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azépine, a prouvé sa valeur thérapeutique dans le traitement des états dépressifs. L'auteur discute les structures chimiques de la promazine et du Tofrānil, et met en évidence leurs différences.

Certaines propriétés physicochimiques de ces deux corps sont comparées. L'auteur expose en outre les résultats de l'étude biochimique du Tofrānil, en particulier la manière dont il se répartit dans les différents tissus chez le lapin.

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PHARMACOLOGICAL STUDIES WITH TOFRĀNIL

E. B. Sigg*

The following report consists of a description and tentative interpretation of the pharmacologic actions of Tofrānil†. As will be demonstrated, Tofrānil is different from other antidepressant agents of current clinical interest insofar as it is neither a stimulant nor an amine oxidase inhibitor. It is also in many respects different from the structurally related phenothiazines.

Results

Effect on the nervous system. Intraperitoneal injection of 1-5 mg/kg of Tofrānil does not increase psychomotor activity in tests on a variety of laboratory animals (dog, cat, rat, mouse). In doses of 5-10 mg/kg, Tofrānil induces sedation in cats and dogs, whereas higher doses are required to achieve a similar degree of sedation in rats and mice. The Tofrānil-treated animals can be aroused from their drowsiness. In contrast to cerebral stimulants (methylphenidate and amphetamine) and amine oxidase inhibitors, Tofrānil does not counteract the sedative effect of reserpine in mammals, although some antagonism seems to be noticeable in rodents. The loss of the conditioned avoidance-escape response induced by reserpine cannot be prevented by pretreating rats with Tofrānil. However, some other signs of the typical reserpine symptomatology such as miosis, ptosis and diarrhea are transiently antagonized by Tofrānil.

When Tofrānil is administered to unanesthetized, paralyzed cats in the same dosage that induced the above-mentioned behavioral changes, the electrocorticogram shows a slowing of frequency and intermittent occurrence of spindles. These changes are first and predominantly noted in the parietotemporal and occipital leads, the fast activity over the sensory motor area being the last to show the change. Very characteristic is the alternation of the slow wave pattern with stretches

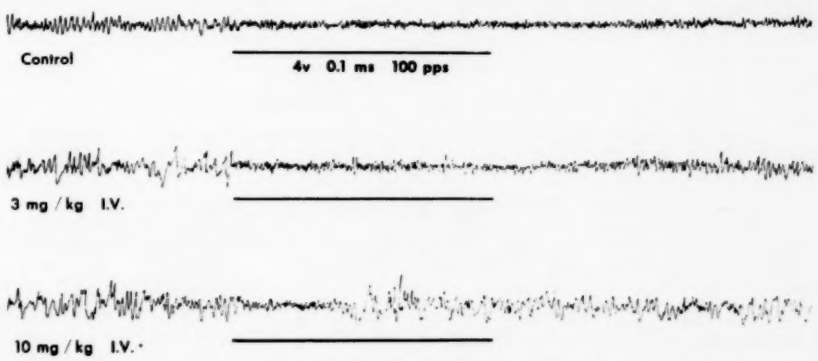

Fig. 1. Effect of Tofrānil on electrocorticogram and activating response.

Intact, unanesthetized cat under succinylcholine and artificial respiration. Bipolar recording from the suprasylvian gyrus.

1. The resting pattern is shown during control, interrupted by a stimulus to the mesencephalic reticular formation, lasting 3 seconds. Note: activating response outlasts the stimulus.
2. Represents record 5 minutes after injection of Tofrānil. Note the higher amplitude and slower frequency of the spontaneous pattern. The reticular activating response does not outlast the stimulus as long as in the control record 1.
3. Additional administration of 10 mg/kg Tofrānil intravenously half an hour after the first injection shortens the activation pattern even more. The high-voltage slow waves are more pronounced.

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†Trade Mark. The generic name of this drug is imipramine. Its chemical designation is 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz(b,f)azepine hydrochloride.

of fast activity. The electrocorticographic activating response elicited either by direct electrical stimulation of the mesencephalic portion of the reticular formation or indirectly by stimulating the sciatic nerve is diminished but not abolished (Fig. 1).

Cortical potentials evoked by presentation of an auditory stimulus in the form of a single click or by single shock to the sciatic nerve are picked up unaltered or slightly enhanced in their respective sensory areas. The threshold for eliciting thalamo-cortical recruiting responses is not significantly altered. In a 'cerveau isolé' preparation the prevailing sleep-pattern is maintained after administration of Tofrānil.

The conditioned escape-avoidance response (1) is fully preserved after single subcutaneous injection of up to 60 mg/kg of Tofrānil (Fig. 2), or after daily oral administration of 30 mg/kg for four consecutive days. This is in sharp contrast to chlorpromazine which leads to an almost total block of the conditioned response after injection of 10 mg/kg subcutaneously.

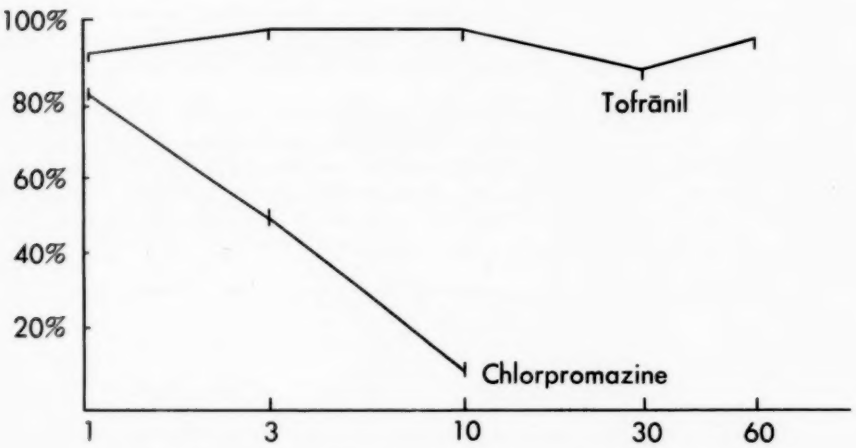

Fig. 2. Effect of Tofrānil on the conditioned escape-avoidance response in rats.
Rats were trained to jump to a pole in response to a buzzer (conditioned response) after having been reinforced to do so in 15 to 20 trials with electric shocks (1). Ordinate: Proportion of group of rats which show the conditioned response. Abscissa: Dose in mg/kg.

Tofrānil potentiates the hexobarbital sleeping time of mice to a much lesser extent than chlorpromazine (Fig. 3). Furthermore, it does not induce sleep in mice pretreated with a sub-hypnotic dose of ethyl alcohol, whereas chlorpromazine initiates long-lasting sleep in these animals (Fig. 4).

Temperature regulation is much better preserved under the influence of Tofrānil than after administration of chlorpromazine. Thus, rectal temperature in mice is maintained near control values after intraperitoneal injection of 10 mg/kg of Tofrānil whereas the same dose of chlorpromazine causes a marked fall in body temperature (Fig. 5).

The susceptibility to seizures evoked by electroshock or pentamethylenetetrazol is diminished by Tofrānil. After injection of 10-30 mg/kg subcutaneously, Tofrānil prevents the occurrence of the tonic phase of the typical seizure pattern in a significant percentage of mice subjected to maximal electroshock or pentamethylenetetrazol convulsions (Table 1). No significant influence, however, is

noted on the fatal course of strychnine-induced seizures. On the other hand, chlorpromazine does not alter the various components of convulsions produced by pentamethylenetetrazol or electroshock.

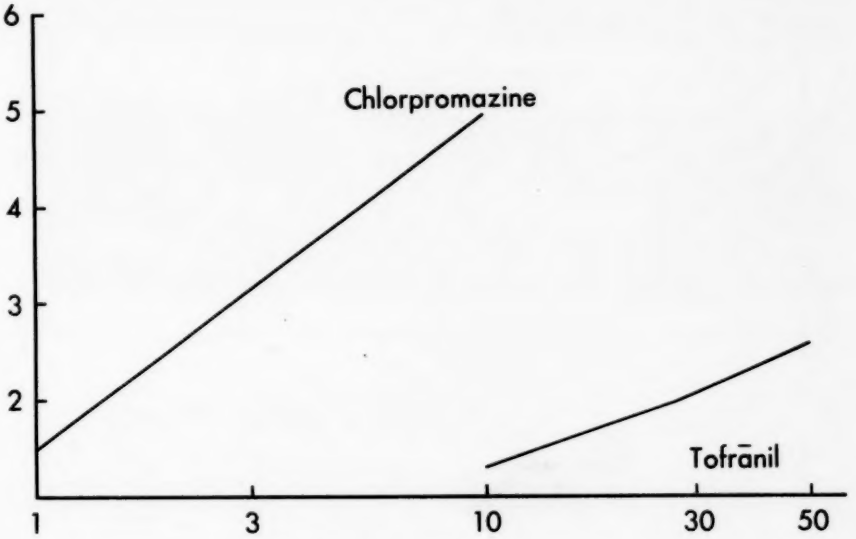

Fig. 3. Effect of Tofrānil on hexobarbital sleeping time in mice.
Ordinate: represents multiples of control sleeping time produced by intraperitoneal injection of 80 mg/kg of hexobarbital sodium into Swiss mice of equal weight and sex. Abscissa: Dose in mg/kg (Tofrānil and chlorpromazine were injected intraperitoneally one half-hour before hexobarbital).

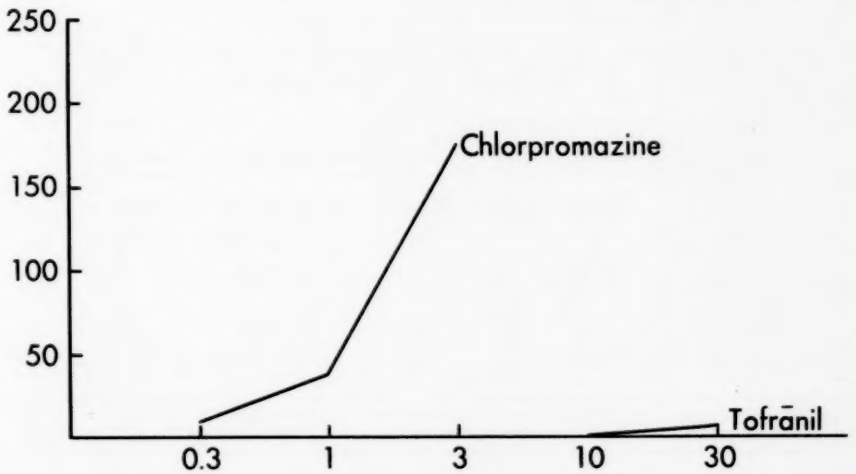

Fig. 4. Influence of Tofrānil on alcohol-induced sedation in mice.
Swiss mice of equal weight and sex received 0.5 ml of 20% ethyl alcohol per 20 grams through esophageal infusion. This dose did not induce sleep in controls. Tofrānil and chlorpromazine were injected intraperitoneally one half-hour before alcohol. Ordinate: Sleeping times in minutes. Abscissa: Dose in mg/kg.

In cats with a high spinal transection the patellar reflex is often enhanced after the first injection of Tofrānil. Subsequent administration of Tofrānil generally fails to reveal any significant change either in mono- or poly-synaptic reflexes (Fig. 6).

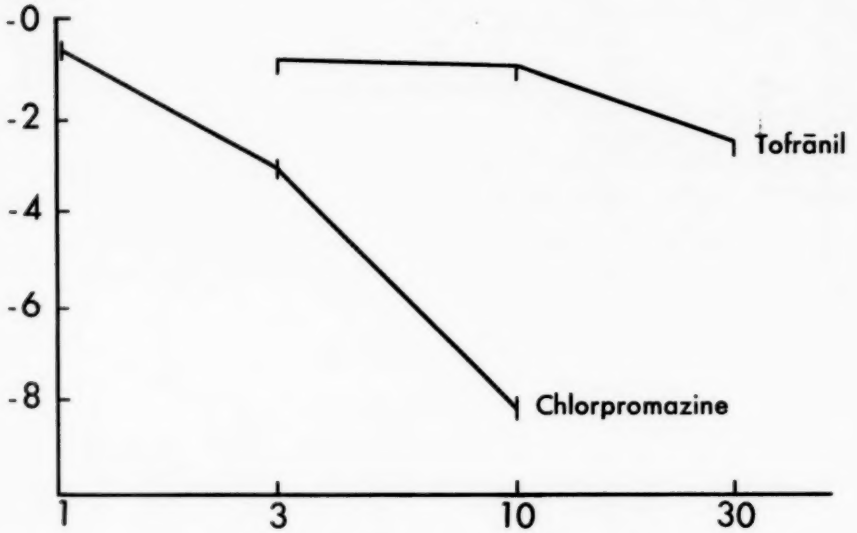

Fig. 5. Effect of Tofrānil on rectal temperature in mice.
Rectal temperature was taken in mice by inserting a thermistor probe 1 cm deep into the rectum. The mice were kept individually in metal containers at room temperature.
Ordinate: Fall of rectal temperature in degrees C. below control level.
Abscissa: Dose in mg/kg (Tofrānil and chlorpromazine were injected intraperitoneally 1 hour before the reading was taken.)

Local anesthetic action can be demonstrated on the rabbit cornea, where insensitivity for 10-20 minutes is produced by topical application of a 1% solution of Tofrānil.

TABLE 1
Effect of Tofrānil on the tonic component of electroshock and pentamethylenetetrazol seizures

Dose of Tofrānil	Electroshock (30 mA/0.2 sec.)		Pentamethylenetetrazol (50 mg/kg i.v.)	
	15 min.	60 min.	15 min.	60 min.
10 mg/kg i.p.	20%	none	none	none
30 mg/kg i.p.	75%	30%	90%	48%

Electroshock was given through corneal electrodes at a current of 30 mA for a duration of 0.2 seconds. Pentamethylenetetrazol was injected intravenously; 0.2 ml of 0.5% solution of Tofrānil was injected intraperitoneally 15 and 60 minutes prior to the induction of seizures. The table indicates the percentage of mice (in a group of twenty animals) which are protected from the tonic component of the full seizure pattern.

Peripheral autonomic, respiratory and cardiovascular effects. Tofrānil in doses of 1-3 mg/kg intravenously does not affect the contraction of the nictitating membrane in response to maximal preganglionic stimulation of the cervical sympathetic

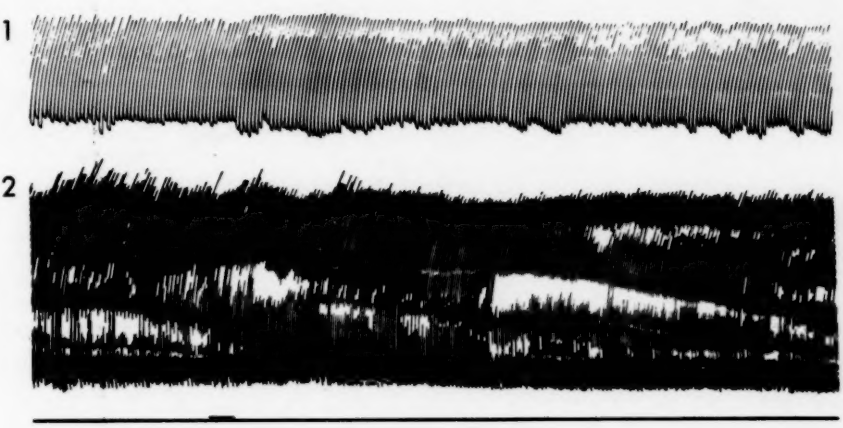

Fig. 6. Effect of Tofrānil on spinal reflexes.
Cat with high spinal transection, maintained by artificial respiration.
1. Flexor reflex: elicited by stimulation of the tibial nerve every 8 seconds and recorded as contractions of the anterior tibialis muscle.
2. Patellar reflex: elicited by tapping the patellar tendon every 4 seconds.
Injection of 3 mg/kg Tofrānil intravenously as indicated by — (45 minutes after a first injection of 1 mg/kg).

nerve. However, higher doses diminish the contraction of the nictitating membrane to both pre- and post-ganglionic sympathetic stimulation to an equal extent, thus indicating that transmission through sympathetic ganglia is preserved under the influence of Tofrānil. Distinct anticholinergic properties are observed after intravenous administration of small doses (1-3 mg/kg) of Tofrānil. Bradycardia and fall of blood pressure induced by stimulation of the peripheral end of the cut vagal nerve are diminished (Fig. 7). Pilocarpine-induced salivation is reduced. Slight mydriasis develops. The effect of acetylcholine in producing spasm of the isolated intestine is also blocked (Table 2) (2). Some of the side effects which are observed under clinical conditions, such as dry mouth, blurred vision, and constipation, can be explained on the basis of the above-mentioned findings.

TABLE 2
Spasmolytic effect of Tofrānil on isolated intestine

Test	Isolated organ	Action equivalent to 1 μg of:	Tofrānil (μg)	Chlorpromazine (μg)
Antihistamine	Guinea-pig ileum	Antergan	4.5	0.38
Antiacetylcholine	Rabbit ileum	Atropine	157.0	140.0
Antiserotonin	Guinea-pig ileum	Phentolamine	0.41	1.0

Doses of Tofrānil and chlorpromazine producing an action equivalent to standard agents are indicated.

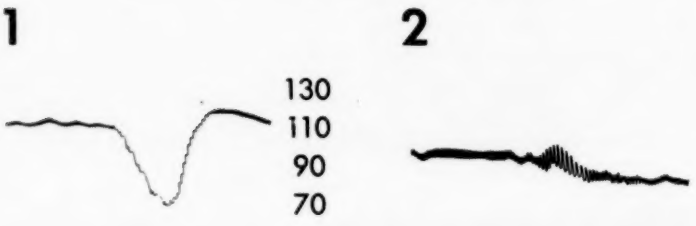

Fig. 7. Effect of Tofrānil on hypotension and bradycardia induced by stimulation of the vagal nerve.
Cat under pentobarbital anesthesia (35 mg/kg i.p.). Stimulation of the peripheral end of the dissected right vagus nerve with square wave pulses of 0.1 msec. duration, 3 volts at a frequency of 100 pps for 5 seconds.
1. Control.
2. Blockade of vagal effect on the heart 15 minutes after intravenous injection of 3 mg/kg Tofrānil.

Respiration in the anesthetized cat is invariably slowed (Fig. 8-A), and the changes in the respiratory reflex normally evoked by stimulation of the central stump of the cut vagal nerve are diminished (Fig. 8-B) as is the carotid occlusion reflex (Fig. 9). In cats lightly anesthetized with pentobarbital, slow intravenous

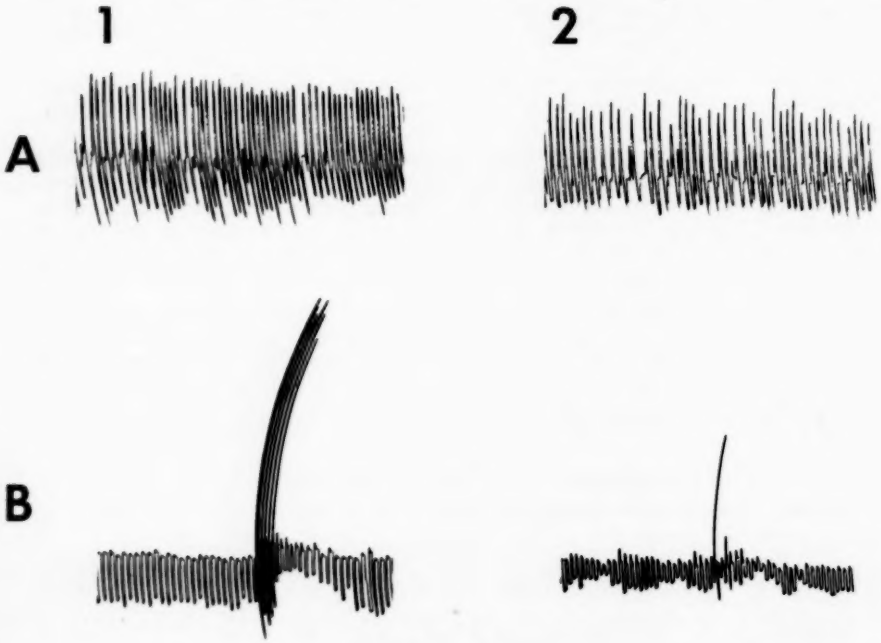

Fig. 8. Effect of Tofrānil on respiration.
Cat under pentobarbital anesthesia (35 mg/kg pentobarbital i.p.). Respiratory activity recorded with tambour connected to tracheal cannula.
A. Spontaneous respiration.
1. Control.
2. 10 minutes after intravenous injection of Tofrānil (3 mg/kg).
B. Respiratory reflex elicited by stimulation of the central portion of the cut vagal nerve with pulses of 0.1 msec. duration, 4 volts and a frequency of 100 pps for 20 seconds.
1. Control.
2. 10 minutes after intravenous injection of 3 mg/kg Tofrānil.
Inspiration down, expiration up. Paper speed: 2 cm per minute.

infusion of 1-3 mg/kg Tofrānil causes a fall in blood pressure of 10-20%. The heart rate is usually not altered but in some instances it is slightly accelerated. Rapid injection of the same dose, however, produces a sharp drop in blood pressure of 40-50%, which cannot be prevented by atropine and/or vagotomy.

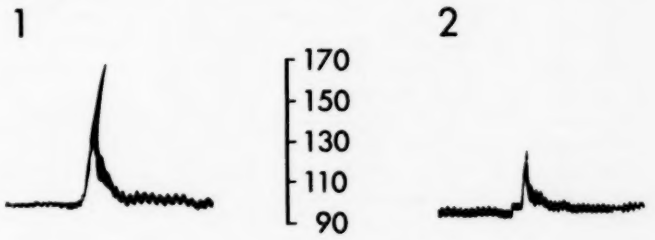

Fig. 9. Carotid occlusion reflex under the influence of Tofrānil.
Cat under pentobarbital anesthesia (30 mg/kg i.p.), bilateral vagotomy.
1. Control (both carotid arteries occluded for 20 seconds).
2. 15 minutes after injection of 3 mg/kg Tofrānil i.v. the carotid occlusion reflex is diminished.

In doses of 1-5 mg/kg intravenously Tofrānil enhances and prolongs the vasopressor response of norepinephrine (Fig. 10-A). Repeated administration does not further enhance the potentiation. On the other hand, the pressor response to epinephrine is initially often reduced but returns subsequently to control values (Fig. 10-B). The rise in blood pressure produced by tyramine or amphetamine is diminished by Tofrānil.

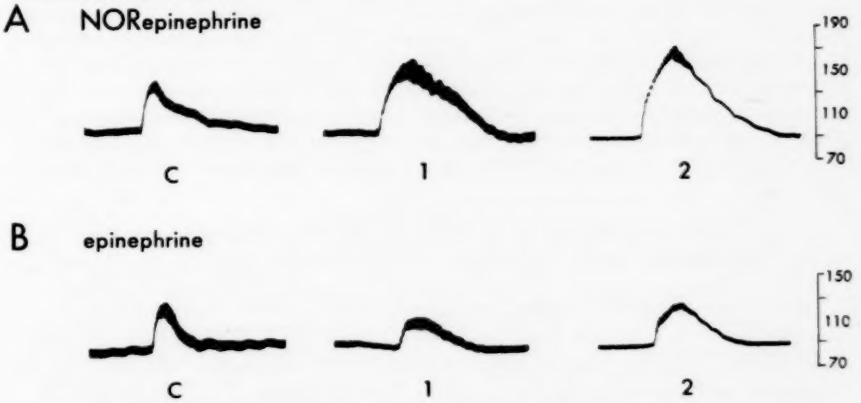

Fig. 10. The effect of Tofrānil on the vasopressor response evoked by norepinephrine and epinephrine.
Cat under pentobarbital anesthesia (35 mg/kg i.p.).
A. Blood pressure response to 2 μg/kg norepinephrine i.v.
C. Control.
1. 10 minutes after 3 mg/kg Tofrānil i.v.
2. 50 minutes after record 1.
B. Blood pressure response to 2 μg/kg epinephrine i.v.
C. Control.
1. 10 minutes after injection of 3 mg/kg Tofrānil i.v.
2. 50 minutes after record 1.

The hypotension elicited in the anesthetized cat by injection of serotonin or histamine is distinctly less pronounced after administration of Tofrānil. This accords with the finding that Tofrānil relieves the contractions of isolated intestine induced

by these two amines (Table 2) (2). The innervated and acutely denervated nictitating membrane reacts with enhanced retraction to norepinephrine after sensitization with Tofrānil (Fig. 11).

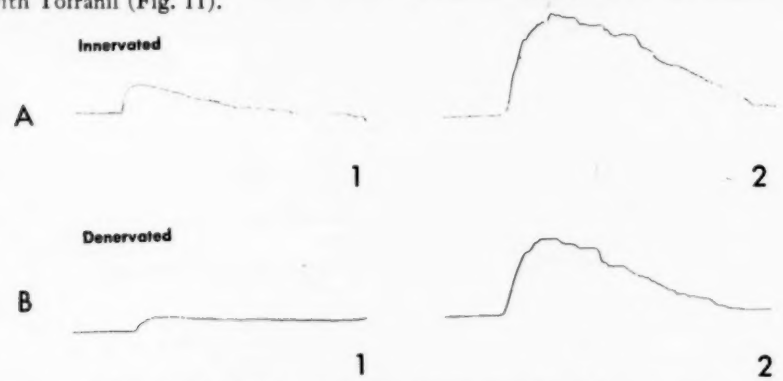

Fig. 11. Sensitization of nictitating membrane to norepinephrine by Tofrānil.
Cat anesthetized with pentobarbital (35 mg/kg i.p.).
3 μg/kg norepinephrine was injected intravenously before (A_1, B_1), and 20 minutes after administration of 3 mg/kg Tofrānil i.v. (A_2, B_2).
Note: Both innervated and denervated nictitating membrane exhibit enhanced contraction in response to norepinephrine after administration of Tofrānil.

Discussion

It is apparent that distinct differences exist between the pharmacologic properties of Tofrānil and the structurally related phenothiazine (1,3). However, the data presented do not offer an explanation as to the mechanisms involved in the antidepressant action of Tofrānil. The finding that Tofrānil does not inhibit amine oxidase (4) indicates that amine oxidase inhibition is not a prerequisite for antidepressant action. In view of its effect on the peripheral adrenergic system the question arises whether Tofrānil exerts its antidepressant effect by sensitization of central adrenergic synapses. Unfortunately, direct evidence for this hypothesis is

TABLE 3
Adrenergic mechanisms which might underlie antidepressant and depressant action

Mechanism	Agent	Effect
Adrenergic transmitter	Norepinephrine	Stimulation
Imitation (of transmitter action)	Methylphenidate Amphetamine	Antidepression
Protection (of transmitter from breakdown)	Iproniazid	
Sensitization (of adrenergic synapses)	Tofrānil Cocaine	
Depletion (of synapse from transmitter)	Reserpine	Depression
Blockade (of transmitter action)	Chlorpromazine	

The hypothesis is offered that Tofrānil might exert its antidepressant effect by sensitizing central adrenergic mechanisms. The position of Tofrānil in relation to other agents affecting these mechanisms is indicated.

lacking. Increasing importance is now being attributed to adrenergic mechanisms operating at the level of the brain stem reticular formation. Thus adrenergic neurohumors, which are highly concentrated in the brain stem (5), stimulate the ascending as well as the descending reticular system, producing cortical activation and facilitation of motor and spinal reflex activity (6). A number of agents, most of them structurally related to catecholamines, produce central excitatory phenomena by acting on the epinephrine-sensitive component of the reticular formation (7). Accumulation of adrenergic neurohumors, their metabolic disposal prevented by the presence of amine oxidase inhibitors (8), leads likewise to an excitatory state. Conversely, depletion of adrenergic neurohumors (9) at their synaptic site (e.g. by reserpine), as well as blocking of their central action, leads to depression. In the light of these considerations it is tempting to speculate that a common denominator for antidepressant activity consists of an activation of central adrenergic mechanisms (Table 3).

Acknowledgement

I am greatly indebted to Misses T. Voegtli and K. Naeff for their valuable technical assistance.

Résumé

L'auteur décrit une série d'essais visant à démontrer les effets pharmacologiques du Tofrānil. Son action sur le système nerveux diffère sous plusieurs rapports de celle des phénothiazines, comme la chlorpromazine, avec lesquelles elle présente cependant une parenté de structure chimique. C'est ainsi qu'une différence a été notée entre le Tofrānil et la chlorpromazine, dans la réponse à un réflexe conditionné (réflexe de fuite), durant la période de sommeil consécutive à l'administration d'hexobarbital ou d'alcool éthylique, dans la régulation thermique et dans la tendance aux crises aiguës.

L'action du Tofrānil sur les systèmes périphériques autonome, respiratoire et cardiovasculaire a été également étudiée. Son effet le plus digne d'attention s'est exercé au niveau du système adrénergique périphérique. On peut donc avancer l'hypothèse que l'action antidépressive est due à une sensibilisation des synapses adrénergiques des formations réticulaires du tronc cérébral.

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Discussion

E. Rothlin*

I appreciate very much the opportunity to participate in this conference where a new psychotropic drug (found by a Swiss firm) will find not its birth but as we say its fire-baptism.

From the foregoing reports we have learned some interesting and important concepts on the phenomenology, psychodynamics and terminology of depression and allied states. This is an impressive picture about the clinical aspects of the problem from the psychological and diagnostic-prognostic viewpoints.

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With the reports on the chemistry and pharmacology of Tofrānil by Dr. Häfliger and Dr. Sigg, to whom I express my best thanks for clearness and timing, we approach the problem from the experimental side. What do we expect from a pharmacological investigation? This should give the basis for clinical evaluation whose goal is to find out the correlations between the changes provoked by psychotropic drugs in human behavior with the alterations produced by such drugs in the neuronal processes in the brain.

Dr. Sigg endeavors to demonstrate the peculiar pharmacological properties of Tofrānil by comparative investigation of the new compound with the classical tranquilizers chlorpromazine and reserpine on one hand and with the central stimulants like amphetamine and LSD on the other. Tofrānil is less sedative than the tranquilizers mentioned and does not antagonize the sedative effects of reserpine, characteristics of amphetamine and LSD. But it counteracts cholinergic symptoms produced by reserpine like miosis, lacrimation and diarrhea, and this corresponds with the anticholinergic properties of Tofrānil.

The most peculiar and selective finding of all the pharmacological tests seems to be the sensitizing effect of adrenergic functions. The data of the anticholinergic and adreno-sensitizing effects of Tofrānil are partly experimental, partly clinical; partly peripheral, partly central.

This is the basis of what Dr. Sigg calls the "antidepressant" activity of Tofrānil. Antidepressive action can be a special kind of alertness or a reactivation of vital processes. It is most probable that this action is related to the autonomic regulatory functions of the brain stem. The localization of these processes only in the reticular formation seems to be too limited. To find out the selective and characteristic properties of Tofrānil, a further and thorough study in the frame of experimental and clinical reference will be probably more reliable than the usual tendency of analogizing with other psychotropic drugs.

Anticholinergic and adreno-sensitizing actions are synergistic in their end-effect, and are outcomings of the general principle of the antagonistic operation of the autonomic nervous sytem in peripheral as well as central nervous functions. W. R. Hess already stressed the importance of autonomic representation in the brain stem and particularly in the hypothalamus for the regulation of autonomic functions in the peripheral effector organs as well as for the relationship between autonomic with somatic and psychic processes. This is the basis of the general concept of W. R. Hess of the ergotropic-trophotropic system which corresponds to the sympathetic and para-sympathetic divisions of the autonomic nervous system.

In this connection I would draw attention to the findings and concepts of Gellhorn, of Funkenstein, Greenblatt and Solomon, and of Darrow and Hill. Gellhorn reports that the fall of blood pressure after mecholyl depends on the reactivity of the sympathetic-adrenal system in relation to the parasympathetic system. Weakness of sympathetic tonus (posterior hypothalamus) *increases*, weakness of the parasympathetic tonus (anterior hypothalamus) *decreases* the extent of the blood pressure drop by mecholyl in intensity and duration. Gellhorn carried out similar investigations with norepinephrine in order to examine the parasympathetic tonus (anterior hypothalamus) and found that the pulse-slowing reflex of norepinephrine is diminished when the tonus of the parasympathetic division is artificially reduced by local application of pentothal.

Many data suggest that the responsiveness of the autonomic centers in the brain stem plays a role in mental disorders, and Darrow and Hill show for instance that central sympathetic reactivity increases as the mental state of the patient improves.

These pharmacological investigations reveal that there are intimate correlations between the regulatory play of the central sympathetic and parasympathetic divisions and that a tonic change of these autonomic centers leads to imbalance of autonomic regulation in peripheral effector organs as well as in neural processes of psychic order.

With regard to the chemical aspects of Tofrānil Dr. Häfliger showed the chemical relation of Tofrānil and promazine and stressed the difference of the ring system, which suffices for the fundamental difference of pharmacological activity. It is worthwhile to mention that Tofrānil and iproniazid are two chemically very different compounds, and yet both agents seem to display *grosso modo* similar clinical effects, and both are used in diverse states of depression. But the pharmacology of iproniazid and Tofrānil seems to be very different with regard to tolerance and the course of action. The mode of action of iproniazid is as far as we know related to its inhibitory action on amine-oxidase. By that the oxidative destruction of catecholamines and of serotonin is inhibited, and this leads to a change in the balance of the so-called neurohumoral mediators, especially in the brain stem. The neurophysiological and biochemical mode of action of Tofrānil is certainly different from that of iproniazid, but is still unknown. So we have an analogous situation for Tofrānil and iproniazid on the one hand and for chlorpromazine and reserpine on the other. Both groups of psychotropic agents are chemically very different but *grosso modo* they produce similar clinical effects.

Yet the mode of action of the two representatives of each group is different too. This statement is of paramount importance because it demonstrates 1) the impossibility of drawing pharmacological and clinical inferences from chemical constitution; 2) the difficulty of explaining behavorial changes produced by psychotropic drugs; 3) the ability to determine if these chemically induced effects are direct or indirect, specific or non-specific, in nature; and 4) the complexity of psychopharmacological problems as a whole.

With a subject like psychopharmacology, in which so many divisions of research are involved and which expands so rapidly, it is not astonishing that theories are flourishing. In this respect, Dr. Sigg is rather cautious. He describes his findings and brings them in relation to the theory of excitatory phenomena by an action "on the epinephrine-sensitive component of the reticular formation;" and he attempts to speculate "that a common denominator for 'anti-depressant' activity consists of an activation of central adrenergic mechanisms."

For the time being the psychopharmacological approach of Dr. Sigg is certainly a good working hypothesis, and corresponds to the above-mentioned concepts of W. R. Hess, Funkenstein et al., Gellhorn, Darrow and Hill, and others.

While the many theories in psychopharmacology are good working hypotheses, proofs of scientific curiosity as well as of the need for integrating understanding, they must be taken as moves in a very great and complex game, the goal of which is to find definite correlations between the psychotropic influence of drugs in human behavior and the physiological, biochemical and psychologic changes produced by such drugs. This can only be reached by more objective experimental and clinical research, accompanied and encouraged by conceptual analysis of the findings.

General discussion from the floor (summarized)

It was brought out in discussion that electroshock and certain phrenotropic drugs such as chlorpromazine induce slow-wave EEG changes in man, while other phrenotropic drugs that are classified pharmacologically as anticholinergic drugs induce desynchronization changes in the EEG. Data were presented showing that Tofrānil is similar in this respect to diethazine and benactyzine, which are known to have anticholinergic activity, and that its therapeutic effect might possibly be related to its anticholinergic activity. The possibility was also mentioned that the ability to diminish convulsive activity might be the common factor in somatic therapy of depression.

One discussant reminded the group that neither a chemical nor a pharmacological approach could have led to a prediction of the clinical effects of Tofrānil, and that these were ultimately discovered by astute clinical observation. However, available methods should now allow us to clarify the manner in which catecholamines may be affected by various drugs. The speaker emphasized the importance of studies directed toward this question, and felt that it was therefore quite worth while to explore Dr. Sigg's suggestions concerning the mechanism of action of Tofrānil.

CLINICAL EFFECTIVENESS OF TOFRĀNIL IN THE TREATMENT OF DEPRESSIVE PSYCHOSES

FRITZ A. FREYHAN*

The question of the pharmacological treatment of depressive states has not only led to a re-evaluation of all therapeutic aspects of depressive disorders but has reopened crucial questions on psychopathology and pathogenesis. The predominant attention focussed on the schizophrenias and psychoneuroses had relegated the affective disorders to a secondary position. The introduction of chlorpromazine sparked off an unprecedented therapeutic and investigative interest in psychoactive drugs. Neuroleptic compounds were found to be uniquely effective in the treatment of disorders of whatever etiology which manifest themselves through a behavioral common path of hypermotility, increased affective tension and hypernormal initiative. Since neuroleptic compounds, through their inhibitory action on psychomotility functions, are specifically potent in reducing excitement and abnormal initiative, they are by virtue of this action useless, if not harmful, for patients with energy deficits and affective retardation.

The search for compounds with antidepressive properties entered a new stage when Tofrānil† was found to differ from the category of antidepressants which are given on the premise of stimulating or energizing action. Clinical experience indicates that states of mental depression differ so widely in phenomenology, incidence and prognosis that drugs with one-directional action, i.e. correcting an energy deficit by stimulation, would seem to be of limited value for broad therapeutic purposes. That the pharmacotherapeutic horizon for depressions remains still cloudy is evident from last month's review of the treatment of depressions in the Mayo Clinic Proceedings (1). The authors, who base their opinion on experiences with dextro-amphetamine, methylphenidate, pipradrol, "meprobamate and benactyzine (deprol)", and iproniazid, state: "The search for an effective drug with which to treat depressions have been prolonged and intensive and in general has been in vain." Electroshock is therefore advocated as "the most effective, safe and rapid method of treatment."

The introduction of a new treatment, an antidepressive drug at that, must of necessity stir up some controversial questions which have remained unresolved in connection with previously established treatments. In the case of the depressive psychoses, we have widely divergent pathogenetic concepts which determine therapeutic rationales. What complicates matters further is the fact that psychiatrists who believe in psychological causation will also avail themselves of somatic treatments, while others with firm convictions on endogenous causation express doubts concerning their effectiveness. Thus electroshock treatment has been widely applied for the purpose of "making the patient more accessible to psychotherapy," while it has only sparingly been used by others who assume a somatic origin of psychotic depressions.

There is little agreement on the nature of the spontaneous course of the depressive psychoses. The question of what constitutes endogenously determined depressive phases is of the utmost significance for the evaluation of therapeutic procedures. This is reflected in the controversial literature on electroshock treatment of depressive disorders. An impressive accumulation of clinical statistics indicates that the treatment of depressions with convulsive therapy is, in the words of Kalinowsky, "the most widely recognized achievement in the field of organic treatment in psychiatry." And to quote Kalinowsky further: "The response of

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†Trade Mark.

depressions to usually less than 5 convulsions, pharmacologically or electrically induced, is one of the most predictable events in psychiatric treatment"(2). Mayer-Gross pointed out that the death rate, whether due to suicide or to the biological consequences of severe psychotic behavior, has been greatly diminished by convulsive therapy (3). Where electroshock treatment was adopted as the treatment of choice, the duration of the depressive phases was found to be drastically shortened, while the long-term prognosis remained uninfluenced.

This is contradicted by authors who maintain that the treatment-induced disappearance of depressive symptoms and the shorter duration of hospitalization are not indicative of an actual change in the spontaneous course of the psychotic process. There is little hope for the assumption that this controversy can be settled on the basis of available statistics. I want to raise the question, however, whether marked differences in the therapeutic management of depressive patients have influenced clinicians' concepts concerning the spontaneous course of the depressive phase. M. Bleuler, for example, writes in 1949, ten years after the introduction of electroshock treatment, that he favors a conservative approach consisting of bed rest, supportive measures and the liberal use of opiates, codeine and sedatives. His objection to electroshock as a treatment of choice is based on its inherent dangers as well as on his doubt of its therapeutic value over spontaneous recovery (4). Bleuler, Kielholz and other continental psychiatrists favor absolute bed rest for severely depressed patients; they also stress the necessity for keeping the patient under the closest possible supervision of nurses day and night, and for sparing the patient the experience of indecision and inhibition by banning all activities and social stimulations (5). By contrast, the depressed patient who enters an American psychiatric hospital is apt to receive every possible encouragement to participate in the social activities in his surroundings. Bed rest is strictly avoided. Suicidal precautions will be camouflaged to spare the patient the experience of supervision. He will receive very active treatment whether electroshock, psychotherapy or, more recently, drugs.

Whatever the merits of either type of therapeutic management may be, it is obvious that the clinicians do not share comparable therapeutic experiences. Moreover, it cannot be excluded that treatment based on psychological and physical inactivation, enhanced by the effects of narcotics and sedatives, may prolong the duration of the depressive states. In all fairness, then, we must assume that therapeutic management of any kind can modify the psychopathology. What constitutes the "natural duration" of depressive phases remains therefore in doubt.

Investigative Aspects

To explore the clinical effectiveness of Tofrānil, or of any antidepressive compound for that matter, poses investigative difficulties. Variation and variability of the clinical features of periodic depressive psychoses in the same person as well as from person to person preclude the establishment of homogeneous clinical groups for comparative purposes. There has been, and continues to be, much controversy on methods of drug evaluation. The primarily observational approach of the clinician has found many opponents. Errors and fallacy, which are inherent in subjective evaluations, are reflected in uncritical claims for inadequately investigated drugs, There is a growing demand for objective methods and statistical validation. But to be objective is not accomplished by rigid rejection of clinical observation and evidence. It must remain the clinical investigator's prerogative to discover drug effects, to identify crucial variables of action and interaction, and to explore the range of clinical effectiveness. We do not have as yet objective methods which are sufficiently comprehensive to portray the multidimensional interactions between personality, psychopathology and drug effect in the unique context of individuality. The clinical

study of drug effect depends on the proper identification of "targets" on which the drug exerts its action. A study of the antidepressive effects of a compound depends, therefore, on the proper selection of patients with suitable psychopathological targets. The effectiveness of the drug can then be measured in terms of its ability to reduce, alter or eliminate these target symptoms. Diagnostic classifications do not suffice to provide essential information on psychobiological and phenomenological differentials. While it is obvious that particular constellations of target symptoms are characteristic for, and indicative of, certain disorders, the symptoms in any given case present only a fraction of the total scale of psychopathological manifestations. In the case of depressive psychoses, for example, it would seem unreasonable to take for granted that the same compound should be as effective in disinhibiting states of psychomotor retardation, as in reducing excessive psychoaffective tension in agitated depressions. It is, therefore, imperative to associate phenomenological analyses with clinical diagnoses.

For the purpose of this report, I have selected from our total Tofrānil series a subgroup of 58 patients whose diagnoses fall within the group of the depressive psychoses. All patients were hospitalized in the Delaware State Hospital. As the only psychiatric hospital for the entire state, its population includes patients from all socio-economic classes, referred as private cases or committed by family physicians and psychiatrists. Multiple hospitalizations during a patient's lifetime mean, with rare exceptions, readmissions to the Delaware State Hospital. The smallness of the state permits close contact between hospital, patient and patient's family after the patient's separation from the hospital. I emphasize this fact to make it clear that observations were not limited to the period of hospitalization.

The investigations were carried out by the hospital's research department. The selection of patients for Tofrānil treatment was based on the diagnosis as well as on specified psychopathological symptoms, the so-called "target symptoms." We distinguish between behavorial, somatic and experiential symptoms. The behavioral category includes such observable phenomena as listlessness, immobility, sadness, agitation or self-mutiliation, to name a few. Anorexia, insomnia, constipation and functional disturbances were grouped under "somatic" symptoms. Thoughts and feelings are listed under "experiential" symptoms.

Daily observational protocols were kept separately by psychiatrists and nurses. Clinical observations, whether by nurse or physician, were unsolicited. In contrast to rating scales which direct the observer's attention to predetermined items, emphasis was placed on spontaneous and unrestricted observation. Although several psychiatrists participated in selection, treatment and evaluations, the author approved each selection, advised on questions of medication and evaluated the patient at frequent intervals. The final evaluations were based on kind and degree of the modification of target symptoms. Thus, evaluations reflect a patient's status at termination of treatment regardless of the clinical or administrative consequences in terms of further hospitalization or separation. The results are divided into 3 groups: optimal, i.e. total disappearance of depressive symptoms, partial modification and failure.

As a matter of principle, treatment was always started by injection. By the end of the first week, oral medication was substituted. There is considerable evidence that the pharmacological effect is more pronounced if the drug is injected. Furthermore, there is always the question of the patient's cooperation in taking the medicine in the desired manner. Uniformity of administration has obvious advantages for comparative evaluations. Injections were resumed when previously satisfactory levels of response could not be maintained on oral medication.

All concomitant somatic treatments were strictly avoided. I want to emphasize this point. I do not see how one can explore the effects of a new compound without

restricting medication to the drug in question. Therapeutic emergencies must, of course, take precedence over investigative principles. If the patient's response is unsatisfactory, this surely calls for a change in dose level or technique of administration rather than for the addition of other drugs. Tofrānil was given sometimes in 2 but mostly in 3 divided doses. The daily dosage ranged from 75 to 450 mg, with an average dose of 225 to 300 mg. Duration of treatment varied from 5 to 193 days, with an average period of 30 to 60 days.

Results

Table 1 presents the clinical sample in terms of diagnoses, sex and age. The diagnostic groups are in accordance with the nomenclature of the American Psychiatric Association. Manic-depressive reactions, depressed type, are psychotic reactions which are fundamentally marked by severe mood swings and a tendency to remission and recurrence. Psychotic depressive reactions differ because of the absence of periodic depressions and marked cyclothymic mood swings. Involutional psychotic reactions are characterized most commonly by depression in the involutional period, without previous history of manic-depressive reaction, usually in individuals of compulsive personality type.

TABLE 1

Composition of clinical sample

Diagnosis	Total	Sex		Age			
		M	F	Under 50	50-59	60-69	70-79
Manic Depressive Reaction Depressed Type	33	10	23	8	7	9	9
Psychotic Depressive Reaction	10	3	7	2	—	6	2
Involutional Psychotic Reaction	15	8	7	2	5	7	1
Totals	58	21	37	12	12	22	12

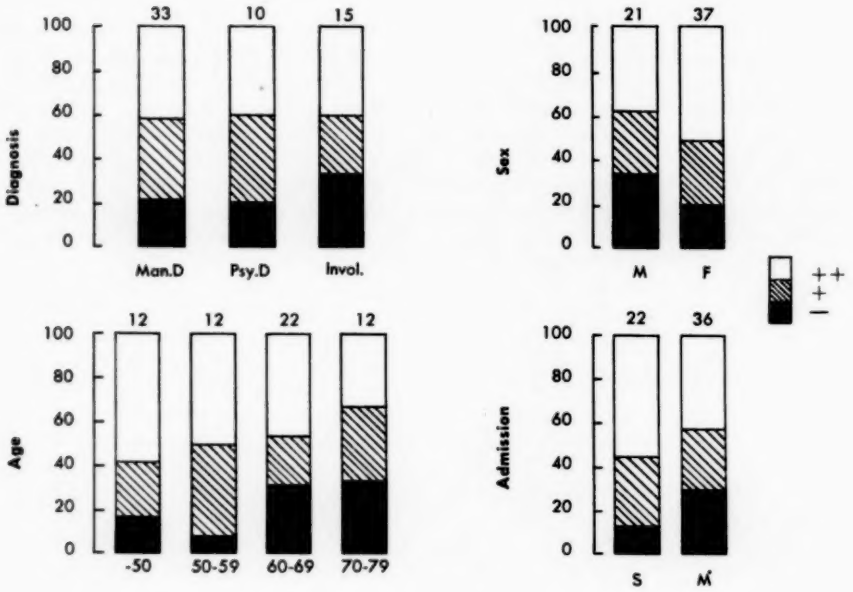
Table 2 presents the results at time of termination of treatment. There are 3 response groups: optimal (++), partial (+) and failure (—). Tofrānil treatment proved most successful in manic-depressive psychoses. Optimal improvement occurred in 51.5%, partial improvement in 27.3% and failure in 21.2%. Least favorable are the results in involutional psychotic reactions which show the highest failure rate (33.3%). The implications of the results will be discussed later. A further analysis of the results based on non-diagnostic variables seems of interest. Relative to sex, there is suggestive evidence that women responded more favorably, having both the highest proportion of optimal results and the lowest incidence of failure. Although it would be premature to attribute prognostic significance to the sex differential, this aspect deserves further investigative attention.

A distributional analysis of results on the basis of age discloses less favorable

responses with increasing age. Since both the first and the last age group consist for the greater part of manic-depressive patients, age rather than diagnostic entity would seem to have some influence on therapeutic outcome.

TABLE 2

Results by diagnosis, age, sex, single and multiple admission



A division according to single (s) and multiple (m) admissions discloses less favorable responses in the multiple admission group. As will be seen later, this is not so much due to the fact of periodic depressions with multiple admissions as to the unfavorable prognoses of particular patients within this group.

An inspection of these results provides significant information on the general trends of therapeutic effectiveness. Nevertheless, this knowledge is of limited value since the results reflect each patient's status at termination of treatment. For a more critical appreciation of these results, we must examine them in the context of both individuality and time. For this reason, I have attempted to document for each patient data portraying the clinical profile from the start of Tofrānil therapy to the present (March 1, 1959). If this seems cumbersome, overly detailed or pedantic, I can only offer as apology my conviction that we may derive more knowledge from individual case analysis than from a sweeping glance at collective tabulations.

Clinical Profiles

The clinical profile tables relate the following data relevant to Tofrānil treatment: age, sex, previous hospitalization, previous electroshock whether ambulatory or during hospitalization. The recorded profile begins with Tofrānil treatment and indicates these subsequent events: separation from the hospital, continued hospi-

talization with or without other somatic treatments, ambulatory Tofrānil treatment, readmission and, in one instance, death.

A few comments about ambulatory treatment, which is also carried out under the auspices of the research department: a research nurse visits the patients in their homes, supervises all aspects of treatment and evaluates the degree of social recovery. Details about this program have been previously reported (6). What I want to stress is the fact that ambulatory treatment is frequently interrupted by placebo periods. This is done to determine whether maintenance treatment is still a therapeutic necessity or should be continued to test its preventive capacity.

Table 3 illustrates the clinical profiles for patients with psychotic depressive reactions. With one exception, all are first admissions. Those with optimal results left the hospital less than 2 months after the start of treatment. One patient (#17) with an optimal result relapsed after 10 months. Another patient (#35) responded only with partial improvement but recovered subsequently on electroshock and insulin treatment. One 77-year-old woman (#44) died in the fourth week of treatment while receiving 225 mg of Tofrānil a day. There had been no clinical improvement during this time. Death, unexpected and sudden, was attributed to coronary occlusion. An autopsy was refused. As in the case of Lehmann, death could neither be associated with the treatment nor entirely excluded.

TABLE 3

Clinical profile: psychotic depressive reaction

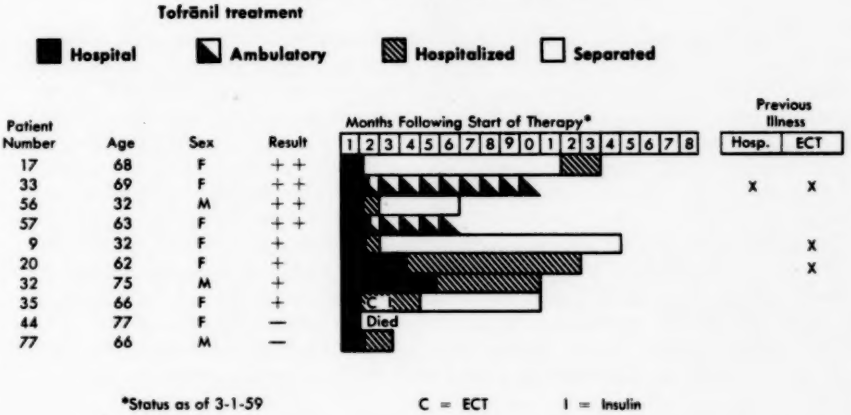


Table 4 illustrates the clinical profiles for the involutional psychotic reactions. The majority of the patients had previous hospitalization, electroshock treatment or both. Patients with optimal results responded early and left the hospital in less than 2 months. Total failure to respond to Tofrānil resulted in early termination in 2 cases, one of which (#43) developed extreme agitation with hallucinations necessitating immediate termination. This patient responded favorably to subsequent electroshock. Two patients (#49 and 79) failed on Tofrānil treatment, but did not respond to convulsive or insulin treatment either. One 74-year-old woman (#21) with a severe involutional depression of many years' duration has shown a conspicuous though only partial improvement, with a prompt relapse when Tofrānil was discontinued. Medication was resumed and is still maintained. This patient was totally retarded and apathetic before Tofrānil treatment. On medication, she converses, shows new initiative, writes letters and participates in social activities.

TABLE 4

Clinical profile: involutional psychotic reaction

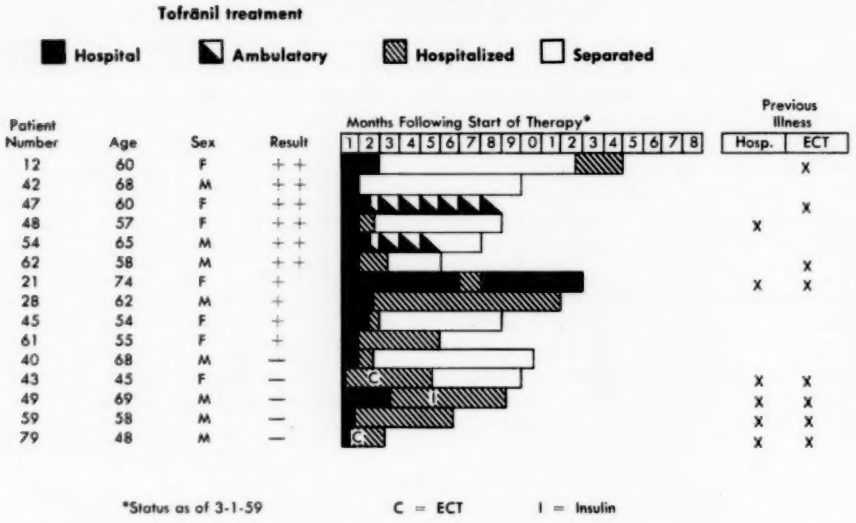

Tofrānil treatment
Hospital
Ambulatory
Hospitalized
Separated
Patient Number
Age
Sex
Result
Months Following Start of Therapy*
1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8
Previous Illness
Hosp.
ECT
12 60 F + + X
42 68 M + +
47 60 F + + X
48 57 F + + X
54 65 M + +
62 58 M + + X
21 74 F + X X
28 62 M +
45 54 F +
61 55 F +
40 68 M —
43 45 F — C X X
49 69 M — I X X
59 58 M — X X
79 48 M — C X X
*Status as of 3-1-59
C = ECT
I = Insulin

Table 5 presents the profiles for the manic-depressive psychoses. As is typical for these disorders, every sort of combination of developments can be found in this series. What seems definitely impressive is the fact that more than half of these patients reacted favorably to pharmacotherapy. Some patients with poor Tofrānil results responded better to electroshock, while others did not. Except for 5 first admissions, all of these manic-depressive patients had from 2 to 10 previous hospitalizations. There is no apparent evidence that the frequency of previous depressions lessened the chances for favorable responses to Tofrānil treatment. The group with optimal responses comprises 17 patients with from 1 to 9 previous admissions. Looking at the profile for the entire group, it becomes evident that pharmacological treatment with Tofrānil, when it was effective, was as therapeutic in terminating the depressive state as had been electroshock during previous hospitalizations. The length of the follow-up period for a substantial number of cases is sufficient to demonstrate that depressive symptoms neither continued nor returned.

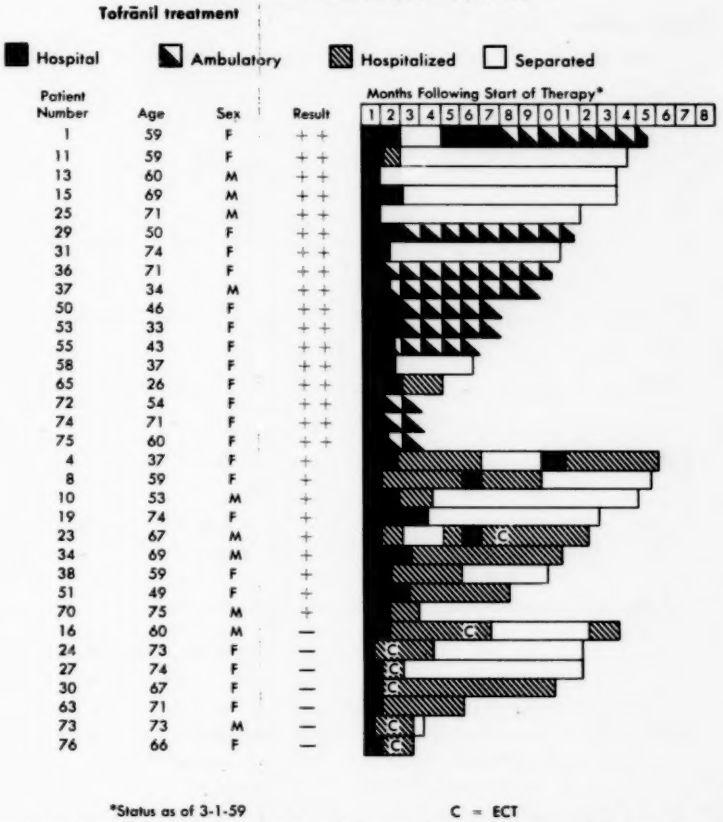
It is obviously impossible to comment on the multitude of developments which are contained in these profiles. They demonstrate rather convincingly, I believe, the immense significance of individual variation which must be taken into account in therapeutic evaluations and investigative methods.

The Therapeutic Mode of Action

How does Tofrānil transact its therapeutic functions? Self-descriptions of the Tofrānil effects on volunteers, reported by Gruenthal (8), are of interest. These persons described various feelings of emotional indifference which they experienced as pleasant since there was no concomitant reduction of drive or initiative. This lends further support to the impression that Tofrānil action differs substantially from the action patterns of both neuroleptic compounds and stimulants. A psychotypical effect in the sense of a drug-induced psychoaffective syndrome is not apparent in patients. What we observe in the initial phases of Tofrānil treatment is

TABLE 5

Clinical profile: manic depressive psychosis

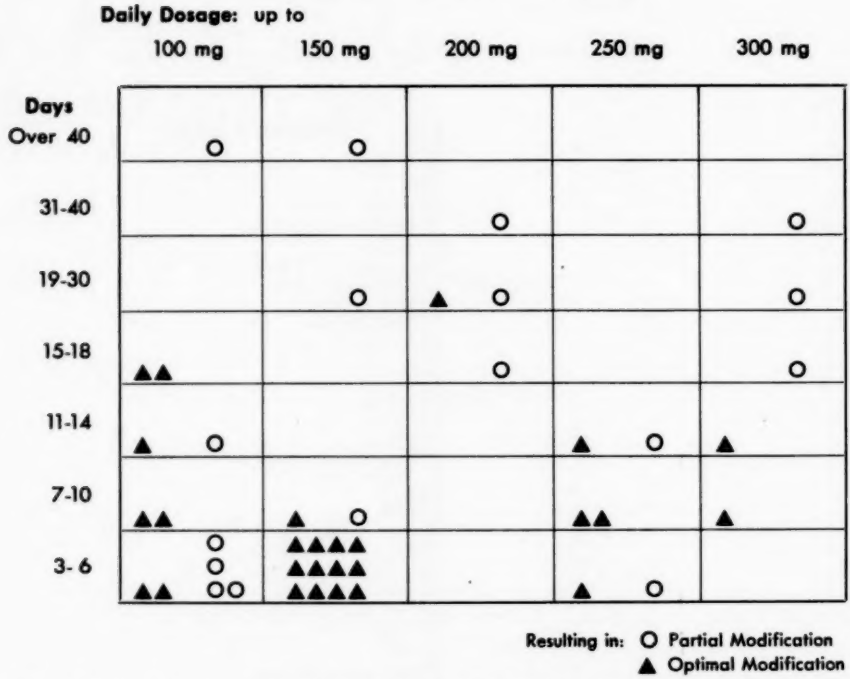


primarily a decrease in the intensity of depressive symptoms. The patient experiences this as a return to normality rather than as a swing of mood (9). Since such a change may be interpreted as an expected development in the natural course of the psychosis, it is imperative to relate this improvement to the duration of treatment. Table 6 indicates when and on what dose level a modification of depressive symptoms occurred. At the time of the first favorable change, one could not predict whether this would result in optimal or partial modifications during the further therapeutic course. What is now, however, quite apparent is the fact that the majority of patients with optimal results are those who responded within 3 to 6 days on 150 mg a day.

I must return to the question: what is the imprint of the Tofrānil effect on depressive dysfunctions? Strangely enough, this is often difficult to define, although most observers — doctors, nurses and, last not least, the patient — agree that a change has occurred. The essence of the transformation, it seems, is not so much reflected in what the patient experiences in a novel manner as in what ceases to disturb him; not the spontaneous expression of new thoughts and feelings, but the attenuation of depressive self-concern is indicative of the pharmacotherapeutic effect. Conversely, if Tofrānil fails, the patient remains as he was. This is in contrast to other somatic treatments and psychoactive drugs which affect every person

TABLE 6

Time of improvement in relation to daily dosage



in a similar manner regardless of final therapeutic outcome. The electroshock-treated patient will show some confusion and disorganization regardless of the eventual favorable or unfavorable response. Patients undergoing insulin treatment show the same evidence of hypoglycemia. Patients treated with neuroleptic drugs manifest a reductive transformation in psychomotility, drive and initiative. Tofrānil, by way of a crude analogy, may be compared with an antibiotic, the action of which only becomes apparent if it hits a suitable bacterial target. Thus, Tofrānil can be thought of as a key which fits only certain keyholes. If it fits, it opens a door through which the depressive psychopathology departs and disappears.

In the absence of identifiable psychotypical effects, there are various somatic manifestations which are indicative of the drug's central mode of action (Table 7). Dizziness and feelings of weakness can be disturbing to patients during the earliest phases of treatment. While there is no evidence of significant hypotensive effects, some patients complain of transitory faintness while walking around. Three patients fell while feeling faint. There were no injuries. A mild impairment of coordination can be observed in those patients who complain of shakiness and display fine tremors of the hands and fingers. One patient developed a *grand mal* seizure on the third day of treatment. This is a chronic patient with alternating manic and depressive phases who has had several courses of convulsive treatment during depressions and neuroleptic treatment during states of excitement. The patient's history revealed an isolated incidence of 3 convulsions in 1929 after an accident.

Somewhat perplexing is the occurrence of paresthesias, both visceral and peripheral. Patients complain of burning sensations in the substernal or epigastric area as well as of numbness and burning sensations on the forearms and hands.

TABLE 7
Somatic reactions due to Tofrānil

Reaction	Number observed	%
Tremors	19	32.8
Rigidity	2	3.4
Weakness	19	32.8
Dizziness	18	31.0
Headache	14	24.1
Shakiness	13	22.4
Falling	3	5.2
Blurred Vision	4	6.9
Drowsiness	4	6.9
Convulsions	1	1.7
Dry Mouth	13	22.4
Paresthesia	10	17.2
Visceral	7	12.1
Peripheral	3	5.2
Perspiration	9	15.5
Tachycardia	3	5.2
Constipation	10	17.2
Allergic Skin Reaction	4	6.9
Vomiting	3	5.2
Diarrhea	2	3.4
Nausea	1	1.7
Edema	1	1.7
Frequent Urination	1	1.7

This is more pronounced during the initial stages of treatment. One patient (#47) developed severe burning and shooting sensations in arms and legs after a very successful response to Tofrānil. This 60-year-old woman had seen various neurologists before her admission to the Delaware State Hospital for treatment of an involutional depression. For several years, she had complained of burning sensation and numbness which had been diagnosed as somatic concomitants of a lingering depression. What seems surprising is the fact that she was free of neurological complaints during Tofrānil treatment. Shortly thereafter, however, she developed very severe sensory disturbances and ataxia. A neurological consultant has now established the diagnosis of multiple sclerosis. A connection between this illness and Tofrānil medication must be considered extremely doubtful.

While none of these somatic effects are severe, they are experienced as more disturbing by those patients who fail to come out of the depressive state. The relatively high incidence of weakness and dizziness in the initial phase would induce many patients to stop taking the drug if treatment were not properly supervised. Since there is nothing particularly "pleasurable" in these drug effects, one may doubt the possibility of drug dependence or addiction.

The analysis of the differential responses of target symptom constellations turned out to be quite difficult; it is still in progress and will be reported in the future. In the case of the neuroleptic compounds, a cleavage between productive and deficit symptomatologies emerged which led to the identification of drug-responsive symptom clusters. In the depressive psychoses, we deal with quantitative and qualitative variations of only a few themes. Agitation versus inhibition, for example, must be evaluated in the psychopathological context in which it occurs. Psychomotor retardation in rigid personalities with involutional psychoses differs from the outwardly similar retardation of self-absorbed, guilt-tormented cyclothymic personalities. Kuhn (10) reported the best responses in cases of "endogenous depression showing the typical symptoms of mental and motor retardation, fatigue,

feeling of heaviness, hopelessness, guilt and despair." Schmitt (11) singled out periodic depressions of the cyclothymic variety as responding most convincingly to Tofrānil treatment. My own data seem to lend support to Schmitt's observations.

The antidepressive action of Tofrānil is selective. The range of this selective action does not coincide with nosological groups nor can it as yet be associated with identifiable individual or psychopathological variables. There remains the interesting observation that Tofrānil, which exerts a calming and certainly not a stimulating effect, does occasionally turn the switch from depression to hypomanic and excited states. This leads me to speculate that Tofrānil fits into cyclothymic keyholes which differ substantially from those of other endogenous depressions. To carry this thought further, we may assume that individual psychobiological factors within the empirically conceptualized diagnostic entities constitute suitable targets for the action of Tofrānil. Perhaps this explains why the therapeutic results are as pronounced in reversing the affective and psychobiological disturbances in some cases, as they are totally absent in others.

Thus far, electroshock is still generally the most effective and most rapid method of treatment for depressions. But there remains the very perplexing fact that patients with electroshock treatment relapse earlier than patients without electroshock. This has been repeatedly reported in the literature. Concerning the manic-depressive patients in this series, the interval between admissions for the group with and without electroshock was without exception longer for those patients who had never been treated with electroshock. While no explanation for this difference has as yet been found, the fact that such a difference exists cannot be ignored.

There are many compelling reasons for the assumption that biochemical methods of treatment will ultimately be superior to physical ones because they will be more specific in acting upon pathogenetic factors. We can only hope that this goal can be reached in the near future. At this time, Tofrānil must be regarded as the first antidepressant drug which manifests a convincing therapeutic capacity.

Résumé

Deux hypothèses opposées continuent à embrouiller le traitement pharmacologique des psychoses dépressives:

1° La dépression résulte d'une déficience biochimique, marquée par la diminution de l'énergie psychocinétique. Elle doit être traitée par des méthodes stimulantes et énergétiques.

2° Les états dépressifs sont des troubles multidimensionnels des fonctions psychobiologiques. Il est impossible de les exprimer sous la forme d'un simple antagonisme.

L'étude clinique des effets du Tofrānil a fait supposer dès le début que ce corps exerçait une activité sélective sur les syndromes dépressifs. On observe rarement une action mentale spécifique, au sens d'un syndrome psycho-affectif provoqué par la médication. Ni l'euphorie, ni la stimulation psychocinétique ne marchent régulièrement de pair avec les effets du Tofrānil sur le cerveau. La caractéristique thérapeutique de ce corps est une dissolution du syndrome dépressif, et une restauration de l'état affectif normal.

Un fait étonnant est que le spectre de cette activité thérapeutique demeure discontinu. Alors que, dès le début des recherches, il a paru évident que le Tofrānil exerce son action optimale sur les dépressions accompagnées d'inhibition, on ne peut pas toujours escompter le résultat du traitement, du fait que certains sujets avec symptômes d'inhibition typiques ne sont nullement améliorés, tandis que d'autres voient leur état se modifier de façon impressionnante.

L'attention des chercheurs s'est concentrée sur l'identification des facteurs psychopathologiques qui semblent particulièrement sensibles à l'action du Tofrānil.

De tels symptômes ont été sélectionnés tant dans le domaine du comportement, que sur le plan psychosomatique et le plan expérimental. Au fur et à mesure des progrès de la thérapeutique, il a été possible de préciser les signes, ou les groupes de signes, susceptibles de modification, ainsi que ceux qui demeuraient réfractaires au traitement. Les appréciations finales sont basées sur l'élimination totale ou partielle des symptômes-clés. Cette analyse phénoménologique s'est avérée très précieuse dans les recherches psychopharmacologiques entreprises pour identifier les effets différentiels des agents thérapeutiques.

L'auteur cherche ensuite à déterminer si l'action thérapeutique est suspensive, correctrice ou préventive. Le matériel clinique comporte en première ligne des malades atteints de psychoses dépressives et hospitalisés. Il englobe, en outre, un groupe de patients en traitement ambulatoire, dont l'anamnèse présente de fréquents accès de dépression. L'auteur cherche, pour finir, à répondre à la question de savoir si les indications relatives du Tofrānil et du traitement électroconvulsif peuvent être formulées. Il se base pour cela sur des expériences de thérapeutique comparée, entreprises avec le même matériel clinique.

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Discussion

K. A. Yonge*

I feel very privileged to have the opportunity of discussing Professor Freyhan's paper. I can join with the majority of the discussants in lamenting that they did not have a prior opportunity of reading their papers. That is by way of an alibi. It absolves one from the responsibility of presenting a prepared contribution. However, I think that Dr. Freyhan has to be commended very highly for the comprehensive nature of his paper and, in particular, for bringing up one or two most fundamental problems.

We took a few turns yesterday on that old "merry-go-round" — what is it that constitutes a depressive illness? As we attempt to distinguish between different types of depression — endogenous, reactive, or neurotic — we sometimes doubt, with the stimulus of Professor Aubrey Lewis, the validity of the distinctions. Dr. Freyhan reintroduces us to the fundamental problem about the nature of depression and I think he has given us some clues as to the direction in which this problem is to be solved.

Early in his paper he reminds us that one aspect of treating depression is "correcting an energy deficit by stimulation." So one concept of the nature of depression is this "energy deficit." Now it seems to me that we have not yet decided among ourselves whether we are going to consider depression at large as a deficiency of energy, with the symptoms as manifestations of this lack of energy, or whether we are going to regard the symptoms as manifestations of inhibition. We are prone to use these very different concepts interchangeably, evidently without realizing their widely different implications. Are we going to say of any particular depression that it is, according to the literal meaning, a lowering or a loss of vitality, with the patient unable to muster energy (whether we regard this energy as psychic or physiological), or are we going to say that the patient has the energy but is in such conflict that its expression, emotional or physiological or both, is blocked? The difference, by analogy, might be be-

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tween the man whose car cannot run because it is out of gas and the man who has the gas and the engine running but holds the brake on. It seems to me that this distinction has to be made clearly in our minds, and perhaps the differentiation of types of depression might hinge more on this distinction.

Before we are going to settle our minds about the nature of the depressive process we shall have to distinguish more precisely the *elements* of the process — the particular elementary manifestations which, in constellation, constitute the depressive illness — the particular signs and symptoms of the illness. Now one of the great merits of Professor Freyhan's paper is that he emphasizes the "need for identification of target symptoms." And he makes an heroic attempt to identify some.

Dr. Freyhan speaks of aiming the therapy at particular target symptoms. I think we can afford to smile at ourselves once in a while for the terminology that we use. This is no criticism of Dr. Freyhan's paper. He is using our customary terms. But we give patients "shots" of medication "aimed" at "target" symptoms. I wonder what "unconscious fantasies" we foster about ourselves in relation to our patients. Would they be of a military or simply a sporting nature?

Anyway, Professor Freyhan very rightly, I think, stresses the need for the identification of the particular symptoms of the illness that we are trying to alleviate, and he attempts to identify some. He is trying to do what a scientist should always do before he attempts to classify his material. First he identifies the elements. The method is most clearly seen in the more simple discipline of botany. The botanist, in the process of classifying his species, first observes and describes the elementary characteristics of his material. Once a constellation of characteristics emerges, then and only then is he ready to apply a collective label — to name a species. Now in our field of endeavour I think we have done what Dr. Freyhan has nicely described as casting a "sweeping glance" at the symptomatology of depression and then hurriedly applied a label — "endogenous," "reactive," "neurotic" and so forth, without ever having got down to identifying and describing in precise and simple terms what are the elementary features with which we are dealing. It seems to me that our psychiatric research is too often hampered, even invalidated, by our inability to define with adequate precision the clinical elements of our material. It is useless to have minutely precise biochemical data at one end of the experiment and loosely defined "target symptoms" at the other.

Dr. Freyhan distinguished between "behavioural, somatic and experiential symptoms," but it seems to me that he ran into difficulties. These categories are evidently on different planes and overlapping — "sadness" under "behavioural" would fit as well or better under "experiential"; and is "insomnia" simply "somatic"? Then the three categories seem to be a mixture of subjective and objective observations — for example, under "behavioural," "immobility" would be for objective evaluation and "sadness" for subjective report. Then some of the features listed are interpretations more than observations — for example, "listlessness" and "sadness." The suggested features are also a mixture of both elementary and complex phenomena, like a mixture of atoms and long-chain molecules — "immobility" and "constipation" would be more elementary, but "thoughts and feelings" are complex. It is no wonder that Dr. Freyhan found, as he said, that "the analysis of the differential responses of target symptom constellations turned out to be quite difficult."

It would be only fair for me, having criticized Dr. Freyhan's attempt to identify the symptoms, to put forward some alternatives. I shall try to suggest a number of elementary characteristics — signs and symptoms—which can be described in simple terms and which are widely indicative of depression. These are all either subjective or objective observations. They are all simple enough to be checked with a "yes" or "no." And some of them would be amenable to at least a rough kind of quantitative assessment on, say, a five-point scale.

As for the elementary *signs* of depression, these are of course those features that are objectively observable by other people: usually the doctor, perhaps the relatives; some of them could be listed under what we might broadly describe as "bodily activity." While we might have difficulty in describing what we mean by depressed facies, because that is so complex, at least we can describe slumped posture — present or absent. We can describe the amount of general bodily movement. That is roughly measurable. We can determine the amount of spontaneity in bodily movement. We can determine non-purposive movements and have some quantitative measurement of these. This could include, for example, the restless activity of the agitated depressed patient. Pacing is sufficiently elementary a feature to include. Handwringing, similarly. Frequency of weeping is roughly quantifiable. Slow gait is an elementary characteristic. The quantity of talk and the spontaneity of talk is roughly measurable. Suicidal or mutilative actions (not thoughts or intentions, suspected or reported) can be clearly elicited and are subject to a "yes" or "no" answer. Early morning awakening is a useful and readily observable feature. Decrease in weight, decrease in food intake and constipation are all fairly precise observable signs.

As for the *symptoms* of depression, if we take simply what the patient said about himself, not concerning ourselves about the veracity of the statements, we can list many simple, elementary features which can be used as a check-list — for a "yes" or "no" assessment; feelings of dejection, worthlessness, guiltiness, deserving to be punished, lack of accomplishment, impending disaster and hopelessness regarding recovery; an unaccustomed pessimistic outlook; restriction of interests (particular interests can be enumerated), "unaccountable" tearfulness, the urge to weep while feeling unable to do so, preoccupation with physical ill-health, preoccupation with dying, contemplation of suicide as a tenable and "best solution," indecisiveness, loss of appetite, loss of taste for food, feelings of fatigue, and a detectable diurnal variation in mood.

This is far from a complete or comprehensive list, of course. I give this only as an example of the discernible elementary features which are a matter of relatively simple observation rather than complex interpretation, and which could be used as more precise target signs and symptoms for our research.

When Professor Freyhan mentioned the difficulties in the analysis of the differential responses of target symptom constellations, he said that the analysis was still in progress and would be reported in the future. I think we shall be eagerly awaiting Dr. Freyhan's further contributions, especially because of their importance in research methodology.

General discussion from the floor (summarized)

The treatment of patients according to target symptoms was discussed. It was stressed that the usefulness of analysis by target symptoms lies in the possibility that constellations of symptoms might respond differentially to various types of therapy, and that such an analysis, while difficult, is worthwhile because a particular treatment need not necessarily lead to general improvement of all symptoms associated with a specific diagnostic category.

Several speakers reported results of treatment with Tofrānil in conditions other than depressive states. In depressed patients with brain damage, ECT was contraindicated and Tofrānil was beneficial. In certain psychosomatic conditions such as mucous colitis, rheumatoid arthritis and essential hypertension, symptoms improved. Schizophrenics with depressive symptoms showed improvement in appetite and in socialization as well as in affect. The consensus was that these improvements were mainly due to improvement of the underlying depression; in fact the purer and more primary the depression the better was the result. On the contrary, patients with pronounced agitation, primary delusional states and previous personality disorders showed poor results.

There was a discussion of dosage, of routes of administration, and of the setting in which treatment was given. The old and the young should have a decreased dose of the drug. Giving the drug intramuscularly was the only way to make sure that the patient was receiving the drug as prescribed. It was safer to hospitalize suicidal patients than to treat them as out-patients; such patients of course required careful observation.

In discussing the safety of Tofrānil, the point was made that in considering the use of any drug in ambulatory patients the physician must satisfy himself that the patient or his family is responsible enough to use the drug properly. No drug should be employed in ambulatory patients who are likely to use it erratically or in excessive quantity.

EFFICACY OF TOFRĀNIL IN THE TREATMENT OF VARIOUS TYPES OF DEPRESSION: A COMPARISON WITH OTHER ANTIDEPRESSANT DRUGS*

J. Delay and P. Deniker**

The changes in the therapy of mental disorders since 1952, due to the introduction of new chemotherapeutic substances and more particularly of neuroleptics, have had little effect on the treatment of depressive states, especially melancholia, for which electroshock (ECT) continued to be in most cases the correct indication.

Nevertheless the indications for ECT are limited for various reasons. The depression may appear too mild or the patient and his relatives may refuse the treatment, a situation which seems to arise with increasing frequency. But the main reasons appear to be that this method becomes less and less effective as the depressive phases follow one another, and that its action is only temporary, as in the case of the increasing number of aged patients so treated. There has therefore been a constant search for a method of chemotherapy of the depressive states either by means of sedative drugs (of which laudanum is no doubt the oldest) or by stimulants acting on the nervous system or on the organism as a whole.

Our interest in this problem was aroused as early as 1949, when in view of the findings of Hyden and Hartelius with malonic dinitrile, we suggested the use of succinic dinitrile, a drug still indicated today for the ambulatory treatment of minor depressions. In 1952, one of us, together with Laine and Buisson, had called attention to the anti-depressant therapeutic effect of isoniazid, and also to the psychic complications occurring in patients treated with it for tuberculosis.

With the introduction of chlorpromazine it soon became apparent that while this drug may be effective in curing simple depressions the picture changes radically in melancholia or endogenous depression; here the effect is principally symptomatic as regards insomnia and anxiety, but the fundamental causes of the depression and the mental suffering experienced by the patient remain unaffected. As to reserpine, our observations were even less encouraging; indeed it is well known that the protracted use of this drug may by itself cause depression and even melancholia. Among the newer neuroleptics, there are two which seem to yield better results in the treatment of depressions: levomepromazine, which will be discussed later, and sulfamidophenothiazine (7843 RP), which like ECT in some cases leads to hypomanic mood inversions but also produces true neurologic syndromes and cannot therefore be recommended as a simple therapeutic method for frequent use.

The results achieved with isoniazid caused us to become interested in the propyl derivative of isonicotinic acid introduced by Kline (iproniazid). The accidents which had been reported in America caused an interruption of our clinical experiments in this direction, but we were nevertheless in a position to confirm the efficacy of iproniazid in the treatment of endogenous depressions or melancholias insofar as the drug can produce a complete reversal of mood, a result which simple chemotherapy had so far only achieved in exceptional cases.

One of the newer anti-depressant drugs is Tofrānil† (imipramine) which differs in chemical composition from both the phenothiazines and isonicotinic acid derivatives. We are indebted to the perseverance of Kuhn for the discovery of the very special properties of this drug as regards depressive states; his findings have since been confirmed by a number of authors, such as Steck and Kielholz in Switzerland, Freyhan and Lehmann on the American continent, Fazio in Italy, and others

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With the assistance of Lemperière, Ropert and others, and basing our work on the general indications suggested by the authors named above, we made an analytical study of the clinical psychiatric properties of the drug. It was our purpose *a*) to define its potentialities with respect to the various forms of depression; *b*) to compare its efficacy with that of iproniazid and levomepromazine; *c*) to find whether it is possible to determine the position of the drug in Delay's classification of modern psychotropic drugs, namely psycholeptics or sedatives, psycho-analeptics or stimulants, and psycho-dysleptics or drugs influencing psychic activity.

Methods and Material

It is a recognized fact that any study of depressive states comes up against the problem of arriving at a simple classification of the cases under consideration. The form, evolution and prognosis of each case are dependent upon a great many factors. Though we do not propose to study these factors here, there are two which have special importance: the symptomatology as observed in the patient, and the etiology of the case. The two often overlap, so that a neurotic patient may at times present a true melancholic syndrome while a manic-depressive person may go through an atypical phase resembling a simple depression or hypochondriac condition. For this reason we included a wide variety of cases, each of which was classified both according to the semeiology and to the available etiologic data. Each patient was first placed in a symptomatic classification limited to 5 categories: 1. Simple depressions; 2. Melancholic depressions; 3. Severe melancholias accompanied by agitation, delusions or stupor; 4. Hypochondriac syndromes; 5. Complex depressions, e.g. those accompanying a psychosis. The next step consisted in listing for each case the main etiologic elements gathered from the case history and from an objective appraisal. Nine such elements were decided upon: A. Reactive or exhaustive depressions; B. Depressions with a neurotic or psychasthenic basis; C. Depressions with a psychopathic or psychotic basis; D. Periodic depressions; E. Depressive phase of manic-depressive disease; F. Depressions of hereditary origin; G. Late depressions occurring after the age of 45; H. Depressions with organic nervous disease; I. Depressions of toxic or endocrine origin.

In this manner, it was possible to identify each case by means of a code, a simple number indicating the semeiologic features and several letters representing the various etiologic elements. As an example, a case of involutional melancholia with signs of organic disease and hereditary cause would be designated by 2 F G H. This system partly overcomes the theoretical difficulty caused by the nature of depressions from the genetic and other aspects.

Of 170 patients treated, 137 were considered suitable for the purposes of our study (all complicated cases were noted). The material included both in- and out-patients and embraced 85 females and 52 males, ranging in age from 19 to 79 years.

Whenever possible, the results of the treatment were recorded daily on a standard form indicating both dosage and the main neuro-vegetative, neurologic and psychic reactions.

Method of Treatment

Treatment was carried out according to three techniques as follows: 1) a majority of the patients were treated by the methods used by the earlier investigators, i.e. the highest dose was given over about 10 days, by intramuscular injections if possible, and then gradually replaced by oral doses, after which slowly decreasing doses were given exclusively by mouth; 2) in some cases where the neurologic and organic state required more careful handling, the dosage was gradually

increased, levelled off and finally decreased again; 3) Tofrānil was administered in combination with neuroleptics (levomepromazine or chlorpromazine) in cases where the anti-depressant drug alone failed to yield satisfactory results or where it was felt that this combination would be more efficient from the start.

Three dosage schedules were used: a normal dosage of 150-200 mg per day, a low dosage of 50-100 mg per day, which seemed more appropriate for older patients, and a high dosage of over 300 mg per day. This latter dose called for considerable caution since most of the severe reactions occurred in cases where it was used.

The duration of the treatment varied from 3 days (in exceptional cases lasting improvement was observed after very brief treatment) to 5 months. Analysis of the results was delayed by the fact that in as many as 40% of the cases the improvement was maintained only by continuing therapy.

Results

The results were evaluated independently by a number of observers and classified as follows: complete remission of the depression (+++); remission incomplete but still satisfactory to the patient (++); marked but inadequate improvement (+); no change, or transient or doubtful effect (0); aggravation (—).

A favorable response often occurs during the first week and is then confirmed after 2-4 weeks, with occasional daily fluctuations. However, the medication has a purely symptomatic effect and maintenance doses must be continued for a long time. In nearly one-half of the cases treatment seems merely to improve the condition until the depressive episode is resolved.

The results have been tabulated and represent the maximum therapeutic effect obtained either with Tofrānil alone or in combination with neuroleptic drugs but not with electroshock. This method admittedly detracts from the statistical purity of the results, but had to be adopted owing to the necessity of giving relief to the patients, in the knowledge that in some cases the condition of melancholia represents a real psychiatric emergency. The results given take no account of later relapses.

The complete results for our 137 patients are contained in Table 1. It will be seen from this table that the proportion of complete remissions is only 22%, but if those substantial improvements which seem satisfactory to the patient even if not to the psychiatrist are added then the proportion reached 60%, which must be compared with the results obtained with iproniazid. The proportion of failures or doubtful improvements, together with aggravations, is less than 20%. In a clas-

TABLE 1

Results	Total	Women	Men
Complete remission (+++)	30 (22%)	16	14
Very marked improvement (++)	52 (38%)	34	18
Inadequate improvement(+)	33 (24%)	22	11
No effect or doubtful (0)	17 (12%)	11	6
Aggravation (—)	5 (4%)	2	3
Totals	137	85	52

N.B.—The results utilized are the optimum ones for each patient, with or without neuroleptics.

sification according to sex there were no significant differences between males and females. Similarly, statistics relating to in-patients and out-patients did not show any appreciable differences. Full details are shown in the tables which follow.

The results arranged according to the symptomatology of the patients treated are given in Table 2. It will be seen from this table that the best effects are obtained in frank melancholic syndromes, where 74% of patients showed results +++ or ++, while in simple depressions only 54% showed substantial improvements, and in severe melancholias only 53%. The lowest figure (47%) is for depressions superimposed on some other psychosis, that is depressions in patients with delirium, or atypical depressions later diagnosed as schizophrenic.

TABLE 2

Symptomatology	Number of patients	Results				
		+++	++	+	0	−
1—Simple depressions	54	12 (54%)	17	15	7	3
2—Melancholic depressions	43	13 (74%)	19	8	3	
3—Severe melancholias	17	4 (53%)	5	3	4	1
4—Hypochondria	6	(67%)	4	1	1	
5—Complex depressions	17	1 (47%)	7	6	2	1
Totals	137	30 (60%)	52	33	17	5

It is of interest to compare these findings with a rearrangement of the results according to the etiologic factors as has been done in Table 3. If the complete remissions and substantial improvements are added together, it is seen that the best results obtained are for the depressive phase of manic-depressive disease (75%), while depressions of hereditary origin reach 68%. This means that the most pronounced effects are in those cases which could be classed as manic-depressive psychosis.

Considerable success was also recorded in depressions appearing after the age of 45 years (67%), or accompanied by signs of organic nervous disease (70%), which mainly represent involutional melancholias and organic depressions, such as those of arteriosclerotic patients. The least successful results are in depressions with a neurotic basis (56%) or psychopathic basis (52%), which is in accordance with the findings shown in Table 2.

The numerical results are amply confirmed by a qualitative clinical evaluation of the patients. The commonest observation is an early improvement, inducing a cooperative attitude by the patient, but then taking a rather slow course. Inhibition and inertia are affected first, mental stress and anxiety are relieved later. In patients who are made worse, fortunately a rare occurrence, anxiety increases and is accompanied by agitation. Even in successful cases insomnia does not disappear at once; often it is aggravated to the extent that barbiturate soporifics have to be given.

TABLE 3

Etiologic factors	Number of patients	Results				
		+++	++	+	0	—
A. Reactive or exhaustive depressions	33	9 (67%)	13	5	5	1
B. Depressions with a neurotic or psychasthenic basis	57	11 (56%)	21	17	7	1
C. Depressions with a psychopathic or psychotic basis	21	4 (52%)	7	6	3	1
D. Periodic depressions	62	13 (61%)	25	19	4	1
E. Depressive phase of manic-depressive disease	12	4 (75%)	5	2	1	
F. Depressions of hereditary origin	28	12 (68%)	7	5	2	2
G. Late depressions appearing after 45 years (including menopausal depressions)	57	13 (67%)	25	11	6	2
H. Depressions with signs of organic nervous disease	20	1 (70%)	13	1	3	2
I. Depressions of toxic or endocrine origin (including puerperal)	11	3 (64%)	4	1	2	1

The drug itself cannot be said to have a euphoric effect, but by inducing a change of mood in depressed patients it causes euphoria and indeed even hypomania, as does electroshock therapy. The reversal in the character of the patient's mood and the reappearance of an interest in life, which most depressed patients complain that they lack, appears to be a characteristic feature of the action of anti-depressant drugs. This fundamental modification is lacking in sedative therapy.

Comparison with Other Anti-Depressant Drugs

Iproniazid. As already stated, iproniazid was the most effective anti-depressant substance among the drugs with which we had experimented before using Tofrānil. Although only 45 suitable cases were treated, observations were made on the lines described above. A comparison of the overall results (Table 4) clearly shows the

TABLE 4

	Iproniazid	Tofrānil
Complete remission (+++)	6 (13%)	30 (22%)
Very marked improvement(++)	16 (35.5%)	52 (38%)
Inadequate improvement (+)	8 (18%)	33 (24%)
No effect or doubtful (0)	14 (31%)	17 (12%)
Aggravation (—)	1 (2%)	5 (4%)
Totals	45	137

superiority of the new compound. The aggregate of +++ and ++ results is 60% for Tofrānil but only 48.5% for iproniazid. Similarly the total of failures and aggravated cases is 33% for iproniazid as compared to only 16% for Tofrānil.

An analysis of the results according to semeiology and etiologic factors shows that the categories in which iproniazid is most effective are practically the same as for Tofrānil, although the results are statistically less significant. It will be seen from Table 5 that only categories 2 and 3 show over 50% of +++ and ++ results. In Table 6 results of this order are over 50% in categories D, E, F and G.

TABLE 5

Symptomatology	Number of patients	Results (iproniazid)				
		+++	++	+	0	—
1—Simple depressions	7	1	2	3	1	
2—Melancholic depressions	24	4	9	3	7	1
3—Severe melancholias	5	1	2	1		1
4—Hypochondria	5		1	1	3	
5—Complicated depressions	4		1	1	2	
Totals	45	6	15	9	13	2

TABLE 6

Etiologic factors	Number of patients	Results (iproniazid)				
		+++	++	+	0	—
A. Reactive or exhaustive depressions	9		4	3	2	
B. Depressions with a neurotic or psychasthenic basis	10	2	2	3	3	
C. Depressions with a psychopathic or psychotic basis	12	1	4	4	3	
D. Periodic depressions	14	2	6	1	5	
E. Depressive phase of manic-depressive disease	10	2	3		4	1
F. Depressions of hereditary origin	10	3	5		2	
G. Late depressions appearing after 45 years (including menopausal depressions)	21	2	9	4	6	
H. Depressions with signs of organic nervous disease	4		1		3	
I. Depressions of toxic or endocrine origin (including puerperal)	2		2			
Not classifiable	2	1				1

If the effects of the consecutive use of the two drugs are compared, Tofrānil again appears superior: in 16 patients treated consecutively with both compounds, Tofrānil proved superior in 11 cases, equally effective in 2 cases and less effective in 3 cases.

Levomepromazine. Several French workers have reported therapeutic success with levomepromazine in depressive states. The most significant and favourable results are those of Letailleur *et al.*, who treated 75 cases. They stress the superiority of the results obtained in cases of simple depressions as compared to severe melancholias, as is usual with the neuroleptics. Nevertheless, of 17 cases of melancholia they report 8 complete remissions and 9 failures or minor improvements, i.e. less than 50% of successes. Our own experience is that even though levomepromazine sometimes results in a real remission of true melancholia, the results are too inconsistent to be reliable. However, these findings have prompted us to combine phenothiazines with Tofrānil in an attempt to improve our results.

Combination of Tofrānil with Neuroleptics

The combination of Tofrānil with neuroleptics, and particularly with levomepromazine, was found by chance to be advantageous. Patients who had failed to respond to Tofrānil reacted very favourably to the combination. In some cases withdrawal tests were significant, withdrawal of the neuroleptic drug causing a relapse and its restoration a renewed improvement.

As already mentioned, the results shown in Tables 1-3 relate to Tofrānil alone or to its combinations. Their analysis is not an easy task. As far as the best results (+++) are concerned, out of 30 patients 15 were cured by Tofrānil alone and 15 by a combination. Of 52 markedly improved cases (++), 23 were treated with Tofrānil alone and 29 with a combination. These figures are clearly not significant, but it must be borne in mind that a fair proportion of the good results obtained with a combination of neuroleptics and Tofrānil were subsequent to complete or partial failure of the latter.

Tables 7 and 8 show the results with 40 cases treated first with Tofrānil alone and then after one or two weeks with a combination of Tofrānil and neuroleptics. Table 7 shows the overall therapeutic effects in the 40 cases under review. It will be seen that in 23 of these 40 cases there was a change from poor to satisfactory results (separated by a double line) as a consequence of the introduction of the combined therapy. In 14 cases no change occurred; in 13 others one category of symptoms was affected, in 9 cases 2 such categories and in 4 other cases 3 such categories. It should be borne in mind, however, that the prolongation of Tofrānil treatment alone might also have been successful.

TABLE 7

	Tofrānil alone	Tofrānil + Neuroleptics
Aggravation (—)	2	0
No effect or doubtful (0)	10	3
Inadequate improvement (+)	26	12
Marked improvement (++)	2	16
Complete remission (+++)	0	9
Totals	40	40

TABLE 8

	1. Simple depression		2. Frank melancholia		3. Severe melancholia		4. Hypochondria		5. Depression accompanying another psychosis	
	Tofrānil		Tofrānil		Tofrānil		Tofrānil		Tofrānil	
	alone	combined	alone	combined	alone	combined	alone	combined	alone	combined
Aggravation (—)			1		1					
No effect or doubtful (0)	4	2	4		2	1				
Inadequate improvement (+)	14	8	7	1	3	2	1	1	1	
Very marked improvement (++)		6		7	1	1	1	1		1
Complete remission (+++)		2		4		3				
Totals	18		12		7		2		1	

Table 8 shows an analysis of the results by syndromic groups. It will be seen that the change from poor to good categories is particularly marked where simple or melancholic depressions and severe melancholias are concerned.

Comparison between Tofrānil Treatment and ECT

Comparative results of treatment with Tofrānil and with ECT cannot be submitted for the reason that the majority of our cases had either failed to respond to ECT or its use was not justified from the start.

Qualitatively speaking, however, there are many differences between the results obtained by the two methods. Although the action of Tofrānil is prompt it is nevertheless slower than that of ECT; the latter seems more effective in severe melancholias where treatment is a matter of real urgency. On the whole there are more similarities in the effects produced than differences, bearing in mind that what is essential is the capacity to bring about a complete change in the mood of the patient.

However, the indications for the two methods of treatment are not quite the same. Those for Tofrānil may be summarized as follows:

(*a*) The immediate use of Tofrānil is justified in the milder forms of depression, where ECT does not appear necessary; this is true even though these milder forms are not those which respond most readily to chemotherapy.

(*b*) Tofrānil is also appropriate in conditions which fail to respond to ECT treatment or become resistant to it. This is notably the case in recurrent presenile depressions.

It has already been found possible to combine Tofrānil with ECT but it cannot yet be said that chemotherapy permits a reduction in the number of shock treatments, although this is our impression. This would be the case in theory, since the continuation of ECT is primarily intended to prevent relapses, a result which may be achieved by chemotherapy, presumably even where the latter had proved inadequate initially.

Among our 137 cases, 19 were given ECT after Tofrānil, alone or in combination, had been found inadequate, with the following result:

(*a*) The effect of ECT was poor (+) or nil (0) in 5 cases, 2 with typical and 3 with severe melancholia. ECT never caused aggravation.

(*b*) In 5 cases (1 of typical melancholia, 2 of severe melancholia, 1 of hypochondria and 1 of depression with psychotic background) there was marked improvement (++).

(*c*) Complete remission (+++) was obtained in 9 cases, 2 of simple depression, 4 of typical melancholia and 3 of severe melancholia.

On the whole there are few cases of depression which prove resistant to both Tofrānil and ECT.

Side Effects

Side effects are extremely frequent but usually of moderate intensity. They rarely interfere with the course of treatment.

Patients complain of various discomforts: dryness of the mouth (one-third of the cases), difficulties of accommodation (one-quarter of the cases, particularly aged persons), dizziness especially when changing position (one-fifth of the cases) and which may even cause the patient to fall when suddenly moving his head. The gait is sometimes unsteady. Other subjective symptoms such as headaches, asthenia, paresthesia, cramps, a feeling of "inner trembling," are less frequent and difficult to assess in patients with anxiety.

The tendency to insomnia has already been mentioned and is often seen in the early stages of treatment. It may call for the use of sleep-inducing drugs. More rarely, patients experience sleepiness in the daytime.

Neuro-vegetative disorders are common: excessive sweating (one-third of the cases), particularly at night, hot flushes, constipation, intense thirst. These disorders are more marked in the early stages of treatment and tend to lessen in intensity later on. Cardiovascular symptoms are very irregular; many patients mention palpitations but there are no objective indications. Hypotension is often observed, however, especially in aged and hypertensive patients. Its importance dictates special caution when using the drug in older patients or those with arteriosclerosis.

Digestive tolerance is good: only 3 patients complained of nausea or vomiting. Cutaneous tolerance is less good: 7 patients developed generalized pruritus, and 2 others transient erythema in various locations. On 9 occasions marked glossitis, with or without stomatitis or sore throat, was observed.

Neurologic symptons are very common: tendinous hyper-reflectivity without clonic spasm or polykinetism (13 cases); muscular twitchings, myoclonia or fasciculations (20 cases); tremors of many different forms (45 cases) such as very fine and quick tremor of tongue and hands, resembling emotional tremor, slower tremor in a resting position with crumbling movements of the fingers but without either muscular hypertonicity or tremors of large amplitude. Dysarthria is comparatively frequent, and micrographia occurs at times. Dysuria occurred in only 2 cases.

On two occasions epileptic fits were observed. In a woman of 38 a generalized convulsion occurred on the 29th day of treatment: this patient had been given large oral doses of Tofrānil of up to 400 mg per day, together with 100 mg of chlorpromazine and 50 mg of promethazine. During the days preceding the convulsion, she had shown a strong generalized tremor. In the second case, a woman of 46 suffered 3 generalized convulsions on the 22nd day of the treatment, followed by stupor lasting 24 hours, with a transient left-side Babinski's reflex. This patient had been four days on a 400 mg daily dose without additional neuroleptics. For some days she

had been complaining of dizziness, visual disorders, tremors and dysarthria. Both these patients later received Tofrānil at lower dosage and showed excellent results.

In 3 patients episodes of dream-like confusion occurred on a dosage of 250 to 300 mg per day. On decreasing the dosage the symptoms disappeared in two of these cases (one male aged 49 and one female aged 65). In the third case, an arteriopathic woman of 56, renewed treatment caused repeated hallucinatory disorders. It should be noted that 3 other patients stated that they experienced visual hallucinations which were clearer with the eyes closed and occurred mostly before falling asleep (colours, small human forms, landscapes). Finally, the inversions of mood observed never went beyond a certain euphoria or very slight hypomania; the frequent use of neuroleptics, however, may have contributed to this decreased effect.

Electroencephalography

The electroencephalograms (by Dr. Verdeaux) which will be discussed in a later publication, have in general shown that Tofrānil produces a marked increase in amplitude of the basic alpha rhythm or a re-synchronization of the latter where before treatment it had been de-synchronized or of low voltage.

When the dosage is increased there is a tendency to hypersynchronization and the pattern slowly becomes acute and "irritative". This occurs only in patients receiving more than 75 mg per day.

This tendency of certain patterns to become "irritative" is a warning that a low dosage should be given to patients whose spontaneous pattern is of this type, for example vascular patients.

Position of Tofrānil in the Classification of Psychotropic Drugs

The investigations which led to the introduction of Tofrānil were initially undertaken in an effort to find new neuroleptics or tranquilizers. This is in line with the neuro-vegetative changes observed, as also with the numbness or somnolence sometimes experienced by patients in the initial stages of treatment.

If an attempt is made to classify the drug according to its main clinical effects it seems inappropriate to place it among the "thymoleptics" (literally drugs which "depress the mood") since its essential action appears to be "thymo-analeptic" in that it is a mood-stimulant. Observations of the effects of Tofrānil on normal persons are not yet available, however.

As we have seen, although the neurologic effects of the drug are by no means negligible, there is no clear-cut syndrome like that characteristic of the neuroleptics. At most there are hyper-reflectivity, tremors and twitchings. The convulsions sometimes observed at high dosage and the electroencephalographic patterns of "irritative" type are quite characteristic of the drug. The mood reversal with expansive euphoria and the occasional hallucinatory complications are similar to the effects observed with isoniazid and iproniazid. The therapeutic action of Tofrānil is comparable with that of the isonicotinic acid derivatives, although the former is clearly more effective and easier to control.

It seems appropriate to class these drugs together as anti-depressive agents falling within the category of psycho-analeptics. Up to now this category of psychotropic drugs was composed essentially of the psychotonic amines whose principal effect is stimulation of wakefulness and anti-hypnotic. However, wakefulness is not the only factor governing the general psychic condition and it is clear that mood regulation also plays a major part.

Psycholeptics or psychic stimulants may therefore be subdivided into 2 groups: (*a*) stimulants of wakefulness or anti-hypnotics, and (*b*) mood stimulants

or anti-depressives. The complete classification of modern psychotropic drugs proposed by Delay is therefore as follows:

1. Psycholeptics:
   - *a*) hypnotics
   - *b*) neuroleptics
   - *c*) tranquilizers.
2. Psycho-analeptics:
   - *a*) stimulants of wakefulness or anti-hypnotics
   - *b*) mood stimulants or anti-depressives.
3. Psycho-dysleptics.

However, this classification must not be regarded as a clear-cut one. Some of the "psychotonic" agents may under certain conditions become psycho-pathogenic or dysleptic; some of the newly discovered neuroleptics may be stimulants; and Tofrānil may be considered to have a secondary sedative effect in addition to its principal stimulant effect.

Conclusions

1. Tofrānil is today the most effective chemotherapeutic drug for the treatment of those depressive states which have hitherto remained relatively unresponsive to simple medication.

2. Good and very good results are usually observed in more than 50% of the cases treated. The highest percentage is found in endogenous, melancholic, presenile and organic depressions, all of which have previously been indications for electroshock treatment.

3. The action of the new drug is somewhat similar to that of electroshock insofar as it can radically modify the depressive mood. Since its action is slower and milder, the indications are somewhat different, and its first use should be in slight or moderate depressions. Long-term therapy with the drug is also possible and this makes it particularly effective in recurrent or lingering depressive states.

4. The combination with neuroleptics, in particular with levomepromazine, seems to reinforce the action of Tofrānil, and improves the results obtained.

5. Therapy is easily managed and although there are many side effects, complications rarely arise. Reactions occur mostly at high dosage or in patients more vulnerable because of age or hereditary factors.

6. Since the principal action of the drug is anti-depressant and mood-regulating, Tofrānil should be classed among the psycho-analeptics or psychic stimulants.

7. Its effectiveness, ease of management and essentially suspensive action indicate that the drug will find long and extensive use, but the attendant risks should be properly weighed if it is to be used by physicians with little psychiatric experience.

Résumé

En rappelant l'inefficacité relative des chimiothérapies neuroleptiques à l'égard des états dépressifs, les auteurs énumèrent les médications qui ont été récemment proposées, avant l'introduction du Tofrānil.

La difficulté de l'expérimentation clinique tient à la multiplicité et à la complexité des états qu'on peut ranger sous le terme de dépression. On a donc adopté une classification à double entrée comportant d'une part un classement syndromique et d'autre part l'indication des éléments étiologiques relevés.

Les résultats, portant sur 137 cas utilisables, sont ensuite exposés en fonction de ces modes de classement. Les meilleurs succès concernent non seulement les dépressions simples déjà influencées par diverses thérapeutiques, mais aussi les états

mélancoliques et dépressions endogènes qui justifiaient l'emploi de l'électrochoc, sans que ceux-ci aient définitivement disparus. L'association de la lévomepromazine à la cure de Tofrānil semble constituer un réel progrès du point de vue des résultats quantitatifs et qualitatifs. La comparaison des résultats obtenus avec le Tofrānil est envisagée avec d'autres substances comme les neuroleptiques et les dérivés de l'acide isonicotinique. Un certain nombre d'observations privilégiées permettent de préciser l'aspect qualitatif du nouveau traitement et son incidence sur divers types de dépressions.

L'examen des effets secondaires est d'une grande importance pour la définition clinique d'un nouveau médicament: à cet égard il ne semble pas que le Tofrānil puisse être considéré comme un neuroleptique malgré la parenté de sa formule chimique. Par contre, l'éventualité de la transformation de l'état dépressif en euphorie expansive (inversion de l'humeur) comme avec l'électrochoc, et le risque — d'ailleurs rare — de complications oniriques et convulsives, contribuent à individualiser le Tofrānil et à le rapprocher dans une certaine mesure des dérivés isonicotiniques.

C'est dans la classe des psycho-analeptiques, selon la classification de Delay, qu'il convient de situer le nouveau médicament. Cette classe comprend deux types de stimulants selon qu'ils agissent spécialement sur la vigilance, comme les amphétamines, ou sur la régulation de l'humeur: ce sont alors des antidépressifs sous le titre desquels on peut ranger les dérivés de l'acide isonicotinique et ceux de l'iminodibenzyle.

Mais par sa maniabilité et son efficacité, surtout en association, le Tofrānil se place actuellement en tête des médicaments antidépressifs. Son usage est vraisemblablement appelé à un tel développement qu'il y a même lieu d'en prévoir les abus.

Discussion*

CAMILLE LAURIN**

Hardly any chemotherapeutic agent has escaped critical analysis by the group at the Sainte-Anne Hospital as soon as it was introduced for clinical use. Professor Delay and Dr. Deniker have provided us with thorough studies on almost all new drugs which are actually used in the treatment of psychiatric conditions. Their opinion is always awaited eagerly. It is based on definition and description of disease entities which have made the French school of psychiatry famous for almost 200 years. Their opinion is characteristically based upon strict criteria, careful analysis and perspective. All possible variables are taken into consideration and it is clear that the authors have a thorough knowledge of the neurophysiology of the brain. It is obvious that the present paper belongs in this same category and utilizes the same criteria. This explains its great value and unquestionable usefulness for all clinicians.

The results presented by Dr. Deniker could hardly be more encouraging. We too are forced to conclude that Tofrānil represents a new and powerful weapon which is easily administered and whose side effects are easily controlled. Despite this important discovery, further studies are necessary to prevent loss of perspective with regard to the danger involved in the treatment of depressions. Within this framework, we have to consider the therapeutic approach and the remaining problems which have to be solved.

With regard to the dangers, we should first mention the danger of suicide. It is well known that this problem always has to be considered in the depressed patient, especially during a period of improvement immediately following institution of therapy. It is necessary therefore that regular medication in appropriate amounts be assured during such a phase if we wish to prevent accidents.

The risk of inappropriate treatment should also be considered. As the number of psychotropic drugs increases, the danger is also increased that psychiatric treatment may become over-simplified. If we are not careful, many clinicians may risk becoming "empiricists" who do not pay the necessary attention to signs and symptoms or to psychiatric observations, which remain as always the basis and the prerequisite of true therapy. Without such strictness and patience, our clinicians also risk becoming "cooks" of psychiatry, completely preoccupied with prepared recipes, adjusting day by day their learned mixture of sedatives, neuroleptics, psychotonics, thymoleptics, etc., solely because of changing symptoms observed during superficial examination.

This means that new ideas are required, indeed as many as possible, and they must be carefully weighed and discussed. Chemotherapy should not eliminate psychotherapy. It should be possible to interpret the dynamics of the psyche in neurophysiological terms. Hereditary and constitutional ele-

*Translation.

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ments should be properly evaluated within the framework of a complete developmental history of the individual and his clinical status. The signs and symptoms should always be critically reviewed so that the best therapeutic approach can be made.

It follows that every patient should be viewed within the framework of his whole existence. This imposes on our science the necessity to develop simultaneously in all directions and to visualize the remaining problems which have to be solved within their mutual relationship. In looking at the forest, one may perhaps never recognize the trees, but if one's outlook is too limited, the trees may be mistaken for the forest.

The presentation of Dr. Deniker shows that there are still numerous problems to be solved. For example the differential diagnosis of the many types of depressions still presents great difficulties. The fact that symptoms and etiological elements are listed in the same table certainly permits eloquent comparisons, but may not represent a final answer to the many questions created by nosological classification. Our experience has to be enlarged, our descriptions have to accumulate, comparisons must be made, and quarrels between schools of thinking must yield to objectivity before we can draw an adequate picture of the many types of depression.

Similarly, if it is true that Tofrānil acts on inhibition and inertia, one should try to explain its lack of action in a certain number (25%) of cases with frank melancholy, where inhibition and inertia dominate the syndrome.

In hospitalized patients who benefit from the action of Tofrānil, it would be interesting to distinguish the part played by the drug, the part attributed to the return to the social and family environment as compared to the hospital, and the part played by psychotherapy, with or without the patient's knowledge, performed by the hospital staff. Finally one can ask how these secondary effects can help us to determine the site and mode of action of Tofrānil.

It should be emphasized that Tofrānil is much more suitable than electroshock therapy for investigating the depressive state. Electroshock constitutes after all a generalized and rapid mode of therapy, where the experimental variables are difficult to control. There is no doubt that the experience gathered by investigators interested in the action of Tofrānil permits better separation of the different variables involved, and also permits consideration of the multiplicity of levels at which the action of the patient and the therapist take place. In this important field of research we eagerly await further contributions from the group at Sainte-Anne Hospital.

EFFECTS OF TOFRĀNIL, AN ANTIDEPRESSANT DRUG, ON ELECTRICAL POTENTIALS OF RABBIT BRAIN

W. G. Van Meter, Helen F. Owens and H. E. Himwich*

Tofrānil† has been reported (1) to be of value in the treatment of psychotic depressions, alleviating the typical symptoms of motor retardation, fatigue, hopelessness and despair. It is also striking that the side reactions were slight and relatively unimportant, though dryness of the mouth, tachycardia and sweating may occur. Despite these promising clinical results relatively little is known in regard to the mechanisms of action of this drug. This investigation is a continuation of earlier basic studies on Tofrānil carried out in this laboratory. We have already shown in rabbits that the EEG arousal reaction to painful stimuli is blocked by Tofrānil (2). Additional electroencephalographic studies revealed chlorpromazine to be synergistic with Tofrānil in preventing EEG alerting, while reserpine is antagonistic to Tofrānil, reversing the Tofrānil depression of the reticular formation and causing EEG arousal (3). The present investigation is an effort to elucidate the stimulating action of Tofrānil.

Method

Observations were made on 15 New Zealand albino rabbits each weighing approximately 3 kg. These animals were prepared in a manner previously described (4), including artificial respiration and curarization. Bilateral EEG tracings were taken from motor and limbic cortices, as well as the hippocampus and amygdaloid nuclei. The route of administration of Tofrānil was the femoral vein, and varying amounts, 1.0, 2.0, 2.5 and 5.0 mg/kg, were administered depending on reactions of the animal until spike-like brain waves or convulsant EEG patterns occurred. Usually the total dosage was 30-50 mg/kg.

Further observations were made on 14 other New Zealand albino rabbits that were tracheotomized under local pontocaine anesthesia and immobilized by curare. After a dorsal area of the skull had been exposed it was trephined bilaterally and silver ball electrodes were inserted through the openings to rest on the sensori-motor cortical areas. These electrodes were held in place by dental acrylic. The sciatic nerve was then exposed and to it was applied an isolation unit stimulating electrode. Stimuli were introduced at the rate of 0.2/sec. with threshold voltages, each stimulus of 5 millisecond duration, until 10 definite cortical responses were recorded. The procedure for stimulation was then repeated 3 times at 5-minute intervals. The drugs, either Tofrānil (5 mg/kg) or chlorpromazine (5 mg/kg) were administered and after another 15-minute interval the procedure was again repeated. The amplitudes of the evoked responses in the contralateral sensori-motor cortex were then measured and compared with the control values. All recordings were made on a Grass Model III D Electroencephalograph.

Results

After injection with Tofrānil, all tracings are changed from those observed in the control rabbit electroencephalogram (5). There is a diffuse increase in amplitude and a lowering of frequency. Occasionally fast activity appears in the beta band. More prominent, however, are the monophasic and biphasic spike-like waves that are observed in the tracings from the amygdaloid nuclei and hippocampus (Fig. 1).

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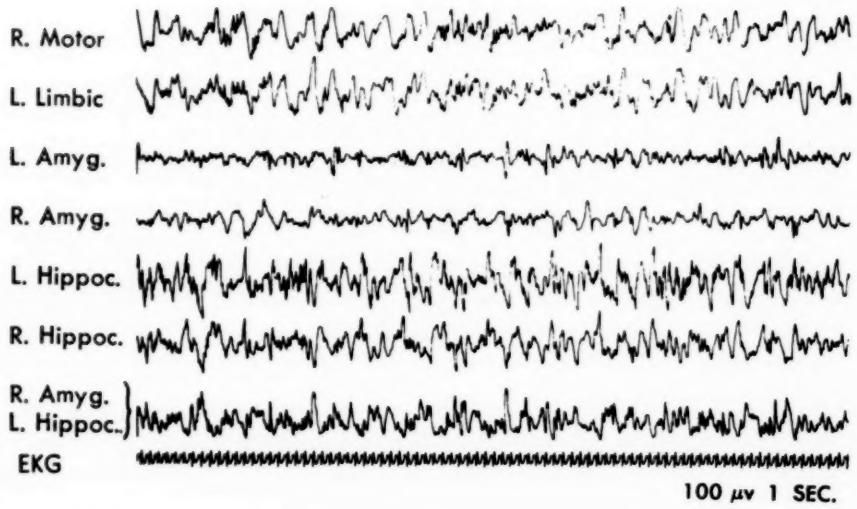

Fig. 1. Preconvulsant dose of Tofrānil (DPID) in a rabbit evoking spike-like brain waves predominant in tracings from the hippocampus and amygdaloid nuclei. Leads: R. Motor — right motor; L. Motor — left motor; L. Limbic — left limbic; L. Amygd. — left amygdala; R. Amygd. — right amygdala; L. Hippoc. — left hippocampus; R. Hippoc. — right hippocampus; EKG — electrocardiograph.

In another experiment (Fig. 2) spikes originating in the hippocampus progressed to a convulsant pattern in that area, spreading to other structures as bursts of EEG seizure activity occurred following Tofrānil.

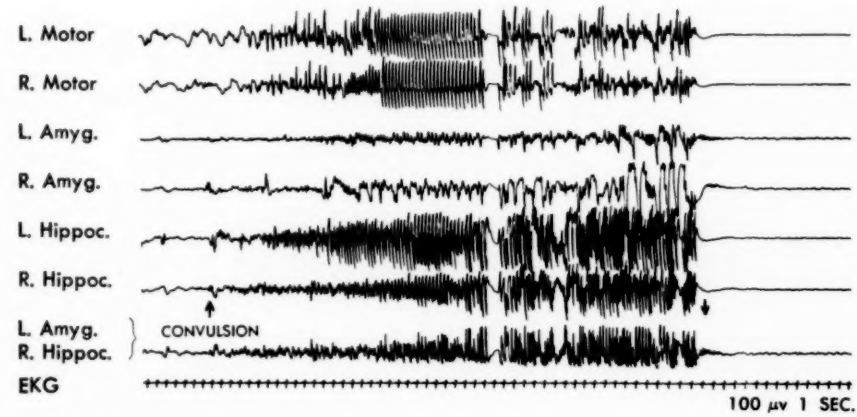

Fig. 2. Spiking starts in hippocampus and amygdala followed by convulsant brain patterns which spread to all leads after injection with Tofrānil (DPID). Leads as indicated in previous figure.

The data on the sciatic stimulation revealed a large increase in the amplitudes of cortical responses significant at the 1% level following the administration of Tofrānil. The change in cortical responses following an injection of chlorpromazine was not as pronounced as with Tofrānil (Fig. 3), with one case out of three being significant at the 5% level, while the other two differences were insignificant.

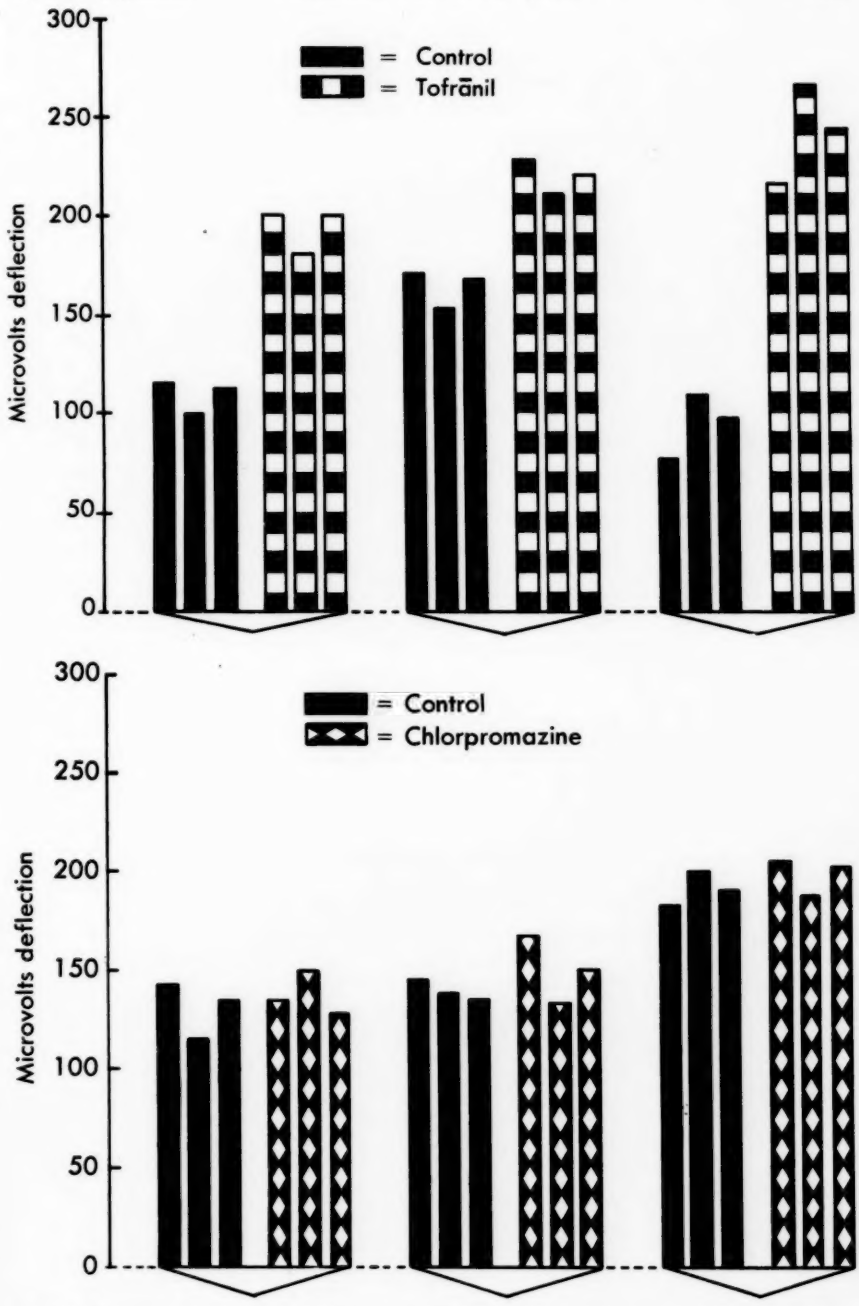

Fig. 3. Bar graph showing results of three typical Tofrānil experiments compared with three chlorpromazine experiments. Each bar represents the average value of the amplitudes obtained from 10 definite cortical responses, expressed as microvolts. Note the greater increase of amplitude following Tofrānil as compared to those with chlorpromazine.

Discussion of Results

In view of the antidepressant effects of Tofrānil, it is of interest that we have found various sites of stimulation induced by that drug. It should be pointed out that the convulsant spikes in the amygdala and hippocampus were obtained with dosages varying from 30-50 mg/kg, while the depression exerted by Tofrānil on the EEG alerting was induced by much smaller doses, 2.5-10 mg/kg. The high dosage required for rhinencephalic stimulation could be attained because the animals were protected by artificial respiration and curare. Perhaps these results can be compared with those obtained on patients who are susceptible to Tofrānil and exhibit amelioration of hallucinatory and delusional symptoms. Similarly, the comparatively rare production of convulsions with Tofrānil may be initiated in rhinencephalic centers. Chlorpromazine also facilitates spiking and convulsions in the cat (6). In the rabbit, despite the use of artificial respiration and curare, we were unable to produce such results, as the animals succumbed to the toxic action of chlorpromazine before the signs of stimulation could develop. It is interesting that both chlorpromazine (8) and Tofrānil (7) may induce seizures, especially in epileptics.

The increased sensitivity of the rabbit cortex to sciatic stimulation as shown by the augmented amplitudes of the evoked sensory responses after the administration of Tofrānil indicates that a lower threshold of that complex system was induced by the drug. Chlorpromazine did not significantly affect this reaction. The comparison between the two drugs is valid because both medicaments block the alerting phenomenon and produce sleep patterns in comparable dosage. If one drug caused the EEG pattern of arousal while the other produced the pattern for sleep, this difference in itself could produce disparate evoked responses. If human patients experience a similar increased susceptibility to stimulation, it could explain in part an action of Tofrānil in combating psychomotor retardation.

Other animal studies coming from this laboratory reveal that Tofrānil can counteract the tranquilization produced by reserpine. Rats and mice premedicated with Tofrānil exhibit an amelioration of the eye-closure phenomenon, a portion of the sedation syndrome affected by reserpine (9). The reserpine-induced decrease of motor activity of rats can also be lifted by Tofrānil (10). But Tofrānil given by itself does not enhance motor activity, and therefore does not resemble amphetamine in this regard.

Some of the hormonal actions of Tofrānil resemble those of iproniazid, another antidepressant. Both drugs raise serotonin (11) and catecholamine (12) levels in the brain. The action of Tofrānil, however, is less marked (9, 13). The hormonal changes evoked by Tofrānil and especially on serotonin, unlike those of iproniazid, cannot be attributed to an inhibition of monoamine oxidase, for Tofrānil does not block the activity of that enzyme significantly *in vitro* (9).

Tofrānil is a complex drug influencing many brain mechanisms, stimulating some while depressing others. Previous results have disclosed that Tofrānil in low doses, 2.5 mg/kg, blocks the reticular formation, evoking a sleep brain wave pattern and preventing EEG alerting (2). Chlorpromazine shares this action with Tofrānil (5). Both drugs diminish the affect to pain whether it is of physical origin or imaginary from delusional or hallucinatory sources. Perhaps this inhibition is achieved in part by the depression of the midbrain reticular formation, thus preventing alerting. In any event, we note this similarity of action with both drugs. In this regard it may be pointed out that their chemical structures exhibit identical side chains (Fig. 4). In contrast, there are fundamental differences in the construction of the nuclei of Tofrānil and chlorpromazine (Fig. 4), and such differences are in accordance with the observation that chlorpromazine is a tranquilizer while Tofrānil is an antidepressant.

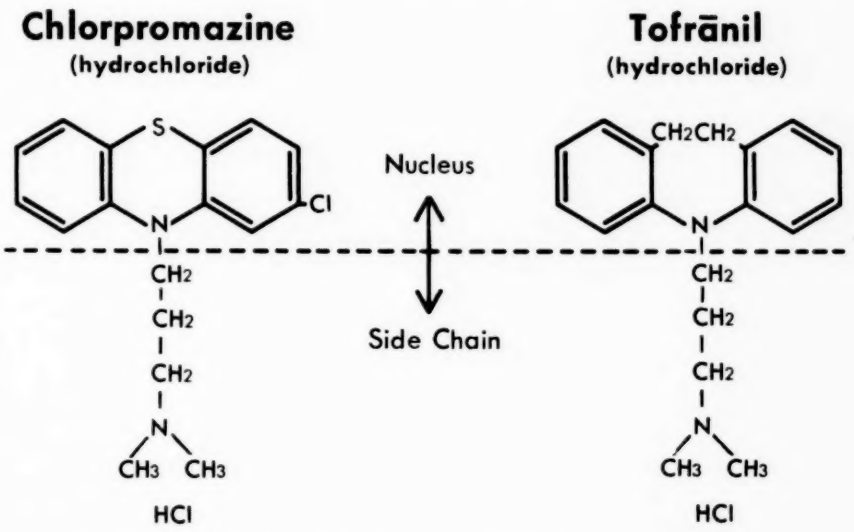

Fig. 4. Structural formulas of Tofrānil (G-22355) and chlorpromazine.
Note (1) the identical side chains of both drugs; (2) a sulfur atom (S) bonds the benzene rings of the chlorpromazine nucleus while an ethylene (-CH_2-CH_2-) group bonds the benzene rings of the Tofrānil nucleus.

Conclusion

A bipartite electrophysiological study of Tofrānil was made, disclosing that this drug increases the excitability of the brain of rabbits. However, when the sciatic nerve is stimulated, the potentials evoked in the sensori-motor cortex are enhanced by Tofrānil in relatively small dosages, indicating a greater sensitivity of this complex system. In addition, Tofrānil in large doses can evoke convulsant spikes in rhinencephalic structures. This spiking may lead to convulsant brain wave patterns which finally extend to all parts of the brain studied. It is concluded that at least for these brain sites Tofrānil acts as a stimulant.

Résumé

Le but de ce travail est l'étude des mécanismes de l'action du Tofrānil, médicament antidépressif. Un des effets de cette action stimulante est de rendre le cerveau plus susceptible, vis-à-vis des stimuli périphériques. L'excitation électrique du nerf sciatique du lapin provoque, dans le cortex sensitivo-moteur, une réaction plus forte, sous forme de potentiels électriques augmentés. Par conséquent, ce médicament accroît l'activité de ce système tout au moins. Il est intéressant de signaler que la chlorpromazine, un tranquillisant, ne produit que peu ou pas d'augmentation de ces réponses corticales. Une autre preuve des propriétés stimulantes du Tofrānil est la présence d'ondes cérébrales en forme de pointes dans le rhinencéphale, c'est-à-dire dans l'hippocampe et les noyaux amygdaloïdes. En fait, si la dose de Tofrānil est trop forte, ces pointes s'étendent à d'autres parties du cerveau, et aboutissent à une crise convulsive. L'emploi de hautes doses, par exemple chez les épileptiques avec dépression associée, doit être surveillée. La chlorpromazine elle aussi peut déclencher des potentiels-pointes et des convulsions chez l'animal; de plus, les doses nécessaires pour produire ce résultat sont moindres que pour le Tofrānil.

L'action du Tofrānil est complexe: stimulante pour certaines zones cérébrales, elle est dépressive pour d'autres. L'électro-encéphalogramme spontané, pris sur l'animal éveillé, est déprimé par le médicament, et se transforme en un EEG semblable à celui du sommeil. Peut-être est-ce là la base de l'action des deux remèdes dans la diminution de la réaction à la souffrance. Ce résultat s'observe, que celle-ci soit réelle (cause physique) ou imaginaire (illusion ou hallucination).

Une partie de la formule chimique du Tofrānil est différente de celle de la chlorpromazine. Il n'est donc pas surprenant que l'un des deux soit un stimulant, et l'autre un tranquillisant. Par ailleurs, les deux corps ont une autre partie de leur molécule qui est identique, et à ce point de vue il est intéressant de constater que tous deux bloquent l'apparition d'une réaction à la souffrance.

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Discussion

A. Hoffer*

The physiological and biochemical history of anxiety and depression is rather brief. It is true ancient Greek philosophers ascribed black moods to certain bodily humours but this was alchemy rather than chemistry. No biochemical theory of anxiety was possible until sympathin was discovered and function assigned to it. The observations that adrenaline can reproduce some features of anxiety ought to have provided a powerful impetus to the biochemists. Perhaps it did but this is not apparent today if one examines the literature.

If I were summarizing the data of the thirties, I would find (1) Cannon's theory of fight or flight or the emergency theory of adrenaline secretion; (2) a clear relationship between adrenaline administration and anxiety. Dr. D. E. Cameron released a series of papers about this phenomenon; (3) compounds similar in structure to adrenaline, e.g. ephedrine and amphetamine, alleviate depression in many people. These findings would lead to the conclusion that the future of biochemistry was bright indeed. What do we find nearly twenty-five years later? We find that psychological, analytical and sociological theorists have been most active until now. Anxiety seems to be most securely established in their bailiwick. The past three years have seen a swing in the pendulum of theory to a more balanced point of view.

This contribution by Himwich, Van Meter and Owens is particularly interesting because it is a continuation of the hypothesis arising from the work of Kluver and Bucy that certain localized areas of the brain have a close relationship to mood. The authors today assume, although they do not so state, that if certain areas of the brain show a special reactivity to Tofrānil as measured by changes in the electroencephalograph, it will indicate how this compound works and, of course, will help us understand where are the brain centers for affect. They find that in rabbits Tofrānil given in low doses (which approximate those used clinically) depresses the alert pattern which should follow sciatic stimulation. Large doses (much above the clinical range) cause EEG stimulation especially in the amygdaloid nucleus and the hippocampus.

Thus it is likely, as these authors suggest, that Tofrānil acts by (but not solely by) depressing the reticular substance. This immediately brings us back to biochemistry, for how else but through some cellular reaction to some chemical can a cell react.

Himwich and colleagues find that Tofrānil increases brain serotonin and catecholamine concentrations, and counters certain aspects of the reserpine-induced depression. At this point I must disagree gently with my learned colleagues who yesterday stated that nothing is known about the causes of depression. I think what they meant was that there is yet no general agreement that a particular factor is the chief cause. My belief is that a great deal is known about chemical causes of anxiety and depression but that these isolated findings have not been unified by an adequate hypothesis.

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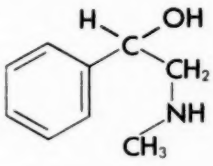
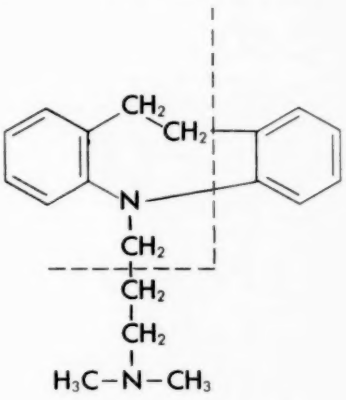
The evidence suggests that the catecholamines must play a vital and perhaps villainous role in the causation of depression:

(1) Adrenaline injection causes anxiety (isopropyl noradrenaline is more active), while noradrenaline does not.

(2) All energizer drugs are related to the catecholamines. (a) Sympathomimetic amines, e.g. amphetamine, methylphenidate, have a similarity in structure to adrenaline; Tofrānil also falls into this relationship as will be seen from the two formulas below. (b) Substances which inhibit enzymes that destroy adrenaline are antidepressants, e.g. iproniazid. (c) Substances which sensitize adrenergic synapses, e.g. cocaine and perhaps Tofrānil.



Epinephrine



Tofrānil

(3) Substances which reduce catecholamines in the brain produce apathetic or anergic depressions, e.g. reserpine. This can be countered by amphetamine or by adrenaline or its precursors but not by serotonin or its precursor, 5-hydroxytryptophane.

(4) Substances which block the transmitter action of catecholamines are depressants, e.g. chlorpromazine.

This evidence suggests very strongly that the catecholamines are the relevent depressant chemicals. Serotonin plays a relatively unknown role as it cannot be related to anxiety or depression. Perhaps Dr. Himwich could tell us which is relatively more important, serotonin or the catecholamines.

This paper provides additional evidence that these amines are important and it tells us where the biochemical difficulty may be located in the brain. I have been "tofranilized" by the enthusiasm of some of the work reported here. Perhaps my judgment, like that of the healthy minded subjects of William James, is somewhat removed from the reality of others. This leads me to believe that the introduction of Tofrānil, which has been so well described at this meeting, marks another break in the darkness and gloom of psychiatric depression.

General discussion from the floor (summarized)

One discussant stated in confirmation of Dr. Himwich that a single injection of Tofrānil significantly increases the level of norepinephrine in the brain. Another discussant mentioned that two groups of disorders could be distinguished on the basis of a differential response to Tofrānil and iproniazid. While typical endogenous depressions responded best to Tofrānil, certain chronic conditions characterized by anxiety, drug sensitivity, and failure to improve after ECT seemed to respond quickly to iproniazid. Dr. Himwich stated in reply that disorders with such distinctive behavioral patterns were extremely useful for analysis of biochemical differences such as differences in serotonin metabolism. Regarding the relative importance of serotonin and catecholamines, Dr. Himwich felt that the question might be best approached by studying precursors of these substances which pass the blood-brain barrier more easily.

EVALUATION OF DRUGS IN THE TREATMENT OF DEPRESSION†

MICHAEL SHEPHERD*

Quantitative methods play a major part in the evaluation of new therapeutic substances. Much of the pioneer work in this field dates from 1931 when the Medical Research Council of Great Britain set up its Therapeutic Trials Committee which soon established the medical statistician as a member of the team alongside the clinician and pharmacologist (1). In the clinical assessment of a new drug it is now generally agreed that after the basic pharmacological data have been acquired from preliminary animal experiments and from pilot trials on human subjects the information should be applied to the measurement of specified reactions against different doses of the drug. It is also necessary to establish the relationship of these reactions to the outcome of the disorder, a step which entails some knowledge of the course of the condition either without treatment or with some other form of treatment. It is then possible to proceed to the organization of the therapeutic trial which, in its classical form, is designed to compare the effects of treatment in two or more groups to each of which there has been random allocation of patients differing only in respect of the treatment administered. The criteria of response to treatment should be as unambiguous as possible and a member of the Statistical Research Unit of the M.R.C. has pointed out that ". . . whenever possible objective and preferably measured assessment of the progress of patients should be used. It is, however, probable that this will have to be supplemented by subjective assessment" (2). Unfortunately the difficulty of standardizing subjective responses, however, has led to their virtual neglect in this field until recent years.

The controlled therapeutic trial is not, of course, necessary for the assessment of all remedies. Such trials can be dispensed with if a previously fatal condition is treated successfully — as in the case of the treatment of tuberculous meningitis by streptomycin — or when the new agent is clearly superior to its predecessors — as in the case of the treatment of scrub typhus by chloramphenicol. Further, ethical considerations may limit the possibilities of a clinical trial in some instances, especially if there is evidence to suggest that irreversible harm could be prevented by the administration of an existing treatment. Nonetheless, in so far as it has introduced the well-tried principles of prophylactic evaluation into experimental therapeutics, the modern clinical trial enforces a healthy respect for scientific method in a field where it has not always been prominent. It is important to remember at the same time that the comparative trial is essentially an epidemiological procedure and reflects the outlook of the statistician, who inevitably tends to think less as a physician and more as a metaphysician, specializing therefore in the description of the types of proof which are appropriate to various types of statement. The commonest form in which these statements are made about the therapeutic value of psychotropic drugs has led to clinical trials designed to answer questions of this order: Are patients suffering from condition X more likely to benefit from treatment A than from treatment B (which may be a placebo)? Whether such a question can be answered with confidence depends in large measure on the precision with which it is possible to define the clinical condition and to specify the criteria of benefit. On both these counts depressive states raise particular problems.

The definition and scope of the illnesses to be treated is of prime importance for the construction of representative samples. No classification of affective conditions in clinical terms can yet be more than provisional, and recent work purport-

†This is an abridged revision of the paper that was read at the Conference.

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ing to distinguish depressive syndromes by means of the mathematical analysis of symptom-clusters has largely confirmed the judgment of clinical experience. There is a wide variation in the estimated frequency of these illnesses based on the most reliable figures we possess, namely the large-scale national statistics of hospital admissions. In England and Wales the manic-depressive psychoses, most of them in the form of depressive states, make up the largest diagnostic group among cases admitted to mental hospitals. By contrast, in the United States and the Scandinavian countries — where hospital statistics are also carefully compiled — the manic-depressive psychoses and involutional melancholia combine to form a relatively small proportion of cases and schizophrenia is the condition diagnosed most frequently. This discrepancy cannot be explained wholly by true differences of prevalence. Idiosyncratic classification is partly responsible: the 'psychogenic psychoses' of the Scandinavian authors, for example, include a number of illnesses which would be regarded as depressive elsewhere. In addition, the traditions of diagnostic practice itself can affect the relative estimates of the two major functional psychoses; thus American psychiatrists appear to be guided more than we in Great Britain by Nolan Lewis's dictum that ". . . the diagnosis of manic-depressive psychoses can be made only by the elimination of schizophrenia" (3). The various prevalence rates of depressive illness provided by responsible workers indicate the need to consider as well the degree of disability leading to inclusion in the diagnostic category. Thus Fremming's surprisingly high figures from the island of Bornholm must be interpreted in the light of his painstaking survey methods and of the finding that 40% of his cases had not been under psychiatric care (4). Our experience in Great Britain has shown that patients suffering from the milder forms of depressive illness have tended to enter mental hospitals in increasing numbers as provision for treatment on a voluntary basis has been extended (5) and that many other cases require extra-mural services for their detection.

It is apparent that if disregarded this clinical diversity will undermine the structure of a comparative trial which depends on commensurate severity of illness in the treated and control groups. But in addition the groups must be homogeneous in respect of outcome if comparison is to be valid. Here the tendency of depressive illnesses to run a self-limiting and often recurrent course renders prognosis difficult in even the better-defined syndromes. It is also necessary to take cognizance of the appreciable mortality rate which is carried by the major depressive psychoses. Norris, for example, has recently shown that the crude death rates for men and women suffering from these conditions are respectively nine and six times the corresponding rates for persons of 16 years or more in the general population (6).

When reasonably homogeneous groups can be constructed, the indices of response have to be defined. The clinical pharmacologist who employs quantitative methods to compare therapeutic substances may proceed by employing one of three methods (7). These are the direct assay, in which measurement is made of the dose just necessary to produce an effect; the measured response of a dependent variable; and the assay by quantal, or all or none, responses which are not measured but recorded as being present or absent. With these techniques it is possible to study dose-response data according to the conditions of the experiment. Unfortunately the disturbances of function which accompany depressive states are insufficiently constant or sensitive to be employed in the way in which, for example, blood pressure can be used in the evaluation of hypotensive agents. This is true even of those physiological indices, like weight and certain autonomic responses, as well as those psychological concomitants like the altered psychomotor reactions, which are related intimately enough to some depressive illnesses to bear on prognosis. 50 years ago Eugen Bleuler commented of melancholia that "the affect is the index of the whole picture" (8) and most of the reported physical and psychological

changes must still be regarded as epiphenomena. For this reason, in our present state of knowledge the outcome of depressive illnesses and the response to treatment have still to be expressed usually in the holistic terms of clinical and social morbidity.

Ethical considerations demand that patients included in a clinical trial should not be deprived of the best available therapy. In many of the milder depressive illnesses this often comprises some non-specific form of pharmacological treatment or some form of psychotherapy. For a large proportion of the more severe illnesses, however, electrical shock therapy is available and cannot be lightly withheld for the experimental testing of a new compound. In all comparisons it is necessary to bear in mind that ECT, which despite much work and speculation remains an empirical procedure, carries a negligible mortality rate and that there are relatively few physical contraindications to its application when administered correctly. It is, nevertheless, a traumatic procedure which many patients and physicians find distasteful. Convulsive therapy has not been subjected to a formal therapeutic trial; most attempts at evaluation have been based on a comparison between the outcome of illnesses treated by ETC in hospital and the outcome of illnesses recorded by hospital controls in the pre-shock era (9). These studies have shown that convulsive treatment reduces hospital mortality rates among patients with depressive illnesses (10) and that it also reduces the time which many of these patients spend in hospital (11). Only 20 years ago mental hospitals could demonstrate the spectacle of whole wards containing " . . . chronic melancholics, who had been in the hospital for two to over twenty years. They had lost the sharp edge of their depression but were anergic, almost inaccessible to stimulation and preoccupied with delusions of unworthiness, hopelessness and physical illness which gravely incapacitated them. Some spontaneously remitted, but there were always others to take their place" (12). This corner of mental hospital life has mostly disappeared following the introduction of ECT. Several workers have since used the duration of stay in hospital as a useful indication of the severity of illness. They have shown that ECT can cut short and fragment many depressive reactions, particularly in the involutional period, but that it does not influence the disease-cycle of the individual patient who exhibits periodic attacks. Further, ECT is without detectable benefit in a proportion of cases from which, on clinical grounds, favourable response would be anticipated.

At the present time there is no pharmacological substance whose efficacy can match that of ECT in the treatment of major depressive illnesses. Many drugs have been tried and found wanting—amphetamine and its congeners, the barbiturates, endocrine preparations, dinitrile succinate, methylphenidate and iproniazid, to mention only a few — but it is now more necessary than ever to specify our expectations of any effective substances which may become available. Even though a drug were to be introduced on an empirical basis it would, of course, be necessary to ensure that it was without serious side effects and that it was of low toxicity. This lesson has been very recently exemplified by iproniazid. If such a substance were no more effective than ECT it would probably find favour because of the advantages attached to its mode of administration, especially if this were by the oral route. In some instances these advantages might prove decisive even if drug therapy were in some measure inferior to ECT, for example in its speed of action. To establish its superiority over electrical treatment on clinical grounds a new drug could be responsible for one or a combination of the following effects: (*a*) it could reduce or abolish the mortality rate associated with depressive illnesses treated with ECT; (*b*) it could curtail the duration of the treated illness or mitigate the social disability still further; (*c*) it could prevent subsequent attacks; (*d*) it could prove to be efficacious in cases which had failed to respond to electrical treatment.

It is important to specify which of these features is being singled out in a comparative trial with ECT. By way of example there may be cited an experiment which we conducted with a drug reputed some years ago to be of value in the treatment of depressive states in the senium. These illnesses display several clinical and biological features in common and we attempted further to secure uniformity by choosing only patients admitted to our own geriatric unit. The patients, most of whom were in their seventh decade of life and suffering from affective illnesses uncomplicated by organic features, enjoyed in general a good prognosis, with an average period of stay in hospital of three months. It had always been the practice in this unit to assess patients for a period of time in hospital before the commencement of active treatment. Advantage was taken of this interval to introduce a double-blind procedure with drug and placebo over a period of about four weeks in which ECT was withheld. During this time blood pressure and weight were recorded, bi-weekly ratings of behaviour were made by doctors and nurses, side effects were noted and different dose schedules of drug were prescribed. Each case was reviewed at the end of this initial period, when the need for further treatment was considered and ECT was administered if it was considered necessary. The relevant results of this experiment are summarized in the table below.

Outcome 3 Months after Admission	Patients given ECT		Patients not given ECT	
	After Placebo	After Drug	After Placebo	After Drug
Discharged well	8	11	1	1
Discharged with symptoms	10	5	5	7
Remaining in hospital	9	12	2	1
Totals	27	28	8	9

Total number of patients = 72.

Though they have not been included in the table the dosages of drug administered were equally distributed among all groups. From these figures it is apparent, first, that most patients required ECT after the trial period on the drug; secondly, that a successful outcome was largely associated with the administration of ECT; and thirdly, that there was no significant difference between the outcome of drug-treated and placebo-treated groups whether electrical treatment was administered or not. It was therefore possible to conclude that in the treatment of depressive illnesses with these characteristics the drug was inferior to electrical treatment and no more efficacious than the placebo.

Relatively precise answers of this type are possible even with empirical remedies, and refinements of statistical method can sharpen such questions by, for example, indicating the degree of improvement which would be accepted as clinically worthwhile before the trial commences (13). If, however, there is a rational basis for the introduction of pharmacological treatment another order of questions becomes possible within the framework of the therapeutic experiment. Thus in a recent study carried out by Pare and Stacey, iproniazid was administered to a group of depressed patients with the objectives of determining not merely whether the

drug was of benefit but also whether those patients who did respond could be differentiated clinically and biochemically (by estimations of urinary 5-hydroxyindoleacetic acid) from those who did not respond and, more specifically, whether among the positive respondents there was any evidence to suggest that their response was related to changes in the brain concentration of 5-hydroxytryptamine (5-HT) or of catecholamines (14). Similarly the recent pharmacological studies which have shed light on the peripheral effects of amphetamine, particularly the liberation of norepinephrine and its 5-HT-like action, have suggested experiments to determine whether these effects are reproduced in the central nervous system of depressed patients responding to this drug. The theoretical importance of such investigations is considerable since the information obtained in a therapeutic setting may be used to shed light on the mechanism of the disorder under study. This model may receive more attention with the accumulation of relevant information about the properties of substances in current use.

The drug treatment of the less severe depressive conditions is beset by problems of its own. These reactions include the large groups of loosely termed "neurotic," "reactive," or "exogenous" depression often admixed with the clinical manifestations of anxiety. Many of them run a chronic, fluctuating course. In such cases depression may represent a symptom as much as a syndrome and the indices of outcome which are available for the major depressive illnesses find limited application in their treatment. Only a minority of the patients require convulsive therapy. If they do attend hospital they are unlikely to require admission and it seems probable that many of them never come under psychiatric care. Recent studies of morbidity in general practice under the National Health Service in Great Britain have suggested that depressive illnesses rank high in the psychiatric case-load of the practitioner and that he treats the majority of patients himself (15). It also seems probable from socio-medical inquiries that other patients suffering from these conditions do not come to medical attention at all but rely rather on the advice of the chemist or on self-medication. When the disability consists of no more than feelings of discontent, distress or discomfort, even social criteria like the work-record may be too crude for purposes of assessment.

It is notoriously difficult to apply the principles of the therapeutic trial to illnesses of this sort. Treatment can be evaluated by a group trial in favourable circumstances (16) but there are many practical and theroretical obstacles. The drop-out rate is high and there is always uncertainty as to whether the patient is taking the drug or not. The diversity within diagnostic groups is considerable and impairs the possibility of generalization from the small numbers which are usually treated. Changes in the course of the condition may be linked more with interpersonal and social factors than with the patient's drug-treatment. The criteria of response in such trials depend moreover wholly or partly on clinical judgments by the observer and ratings of experience or drug-preference by the patient, criteria which are inevitably subjective. Finally, the wide individual variation of response to drugs (17) assumes such importance that it may be necessary to employ an experimental design which enables the information about individuals to be extracted.

An alternative method of tackling this problem is to concentrate directly on the universe of the individual patient and to study the intra-individual variation. This principle is familiar to physiologists and psychologists (18, 19). Its application to therapeutics has been advocated by Hogben as a means of direct examination of the stimulus-response nexus. What he calls the self-controlled, self-recorded trial is designed to study therapeutic response in states of chronic, low-grade morbidity which are not regarded as reversible and where the end-points of therapy are defined by symptomatic relief rather than by cure (20). The controlled investigation of subjective data in the form of symptoms is a central feature of the experimental

design. Symptoms are subdivided for the purpose into those which are usually associated with disturbances of behavior and so become open to observation, for example, anorexia, and those in which personal experiences predominate and render the subject's testimony the principal source of data, for example referred pain. Our experience suggests that the treatment of less severe chronic depressive states can be investigated in this way. The suitable subject is invited to complete pre-designed forms bearing on specified functions and experiences. The form can be filled in at regular intervals in normal working or domestic conditions. Internal checks are provided for subjective data, and the co-operation of an observer can be enlisted for the verification of functional disturbance. After a period of observation without treatment the effects of medication can be observed, the subject remaining in ignorance of the substance which he receives.

If the initial recordings are made in hospital the nursing staff will enable an estimate to be made of the reliability of the subject's observations. On discharge the subject's spouse can co-operate in the same way for regular recordings in the intervals between psychiatric assessments. Though the technique raises several problems in the selection of subjects, the recording of information and the mathematical treatment of summated indices, the data which it provides about natural fluctuations and the continuity of response make it a promising research tool in the study of these elusive conditions.

It now seems probable that we are soon to be presented with so many new anti-depressive compounds that the familiar clinical attitude of *laissez-faire* empiricism will be increasingly difficult to sustain. The clinician is compelled to hold the balance between the scales of laboratory data on the one hand and stochastic theory on the other. Though his experience and judgment are essential it will be necessary for him to adopt a more experimental role in the future if he is to cooperate fully with the pharmacologist and the statistician, whose techniques he should understand if full weight is to be given to observations made in the clinical setting. More clinical research is indispensable to progress in the evaluation of drugs for the treatment of depression.

Résumé

Les épreuves cliniques, qu'elles soient cliniques ou comparatives, comprennent tous les éléments qu'il y a lieu d'observer pour l'appréciation d'un médicament nouveau. Des facteurs cliniques et éthiques déterminent jusqu'à quel point ces éléments peuvent être pris en considération. L'évaluation des substances médicamenteuses utilisées dans les états dépressifs doit tenir compte: *a*) de l'hétérogénéité probable du matériel d'étude; *b*) du petit nombre d'indices mesurables permettant de juger de l'effet du traitement, spécialement dans les cas les moins graves. Toute thérapeutique médicamenteuse des dépressions doit pouvoir supporter la comparaison avec la thérapeutique par choc électrique. Même s'il s'agit d'un remède empirique, son efficacité relative doit être précisée et rapportée aux résultats bien connus de l'électrochoc. Si la médication est entreprise sur une base rationnelle, les résultats du traitement peuvent avoir une grande importance théorique. Dans le cas de la dépression, affection relativement peu aiguë, de nombreux obstacles se dressent sur le chemin d'une épreuve de groupe, et la composante subjective de la maladie acquiert une importance majeure pour l'évaluation de la thérapeutique. Une expérimentation clinique auto-contrôlée et auto-enregistrée peut être tentée dans cet ordre d'idées.

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Discussion

R. Bruce Sloane*

I very much enjoyed Dr. Shepherd's paper and considered that he made a good case for controlled drug trials. Such studies seem to have undergone a kind of historical waxing and waning. Thus prior to the last decade or two, one seldom heard of them. Once they entered the scene, however, it became fashionable to decry results that were not "controlled" in this manner. But now the wheel has, as it were, turned full circle so that it is fashionable, even perhaps avant garde, to heap critical coals of fire upon such an approach. Thus, the double-blind study has been compared by Tuteur (1) to an illusion. He instances the so-called "objectivity" and says that judgment must be made without any possibility of bias, without any overcompensation for a possible bias, and without any possibility of the accusation of a possible bias. Naturally, he concludes with an impossibility: that such objectification is impossible, and not only impossible but unrealistic and perhaps also unrevealing. Other investigators believe that any such control is against their ethical dictates, others again that only by an intimate knowledge of the psychopathology of one patient can a true understanding of a drug's action be reached. At the other extreme lies the investigator who, mole-like, tunnels down his double-blind burrow, neglecting information, but secure in his belief in the safeguards of his methodology, as though everything will be revealed in the ultimate statistical wash.

Both attitudes seem to me to be based upon misconceptions of the difficulties involved in clinical trials. Whether these be of psychiatric or other patients, the problem lies in an attempt to separate out all the multitudinous factors involved in the therapeutic procedure. We are unable to exclude these variables and therefore must take cognizance of them. Thus, we have heard a great deal about the patient and the lack of knowledge of the aetiology of his illness, which in itself may take many shapes and forms. We have heard talk of the milieu in which the treatment occurs, the so-called psycho-social factors. However, we have heard little of the therapist who is administering the treatment. If we take into account that there are widely differing therapists, we also have to take into account that they may need to use the same drug and therefore wish to know more about its specific pharmacological action. Thus, by temperament, certain investigators seem more able to stand aloof and observe their patients, perhaps from the end of the ward, their critics will say, in contrast to others who plunge in with great enthusiasm, using their drugs almost as extensions of their own body image.

It is perhaps easier to see the symbolic value of the drug to the patient than to the doctor. However, it becomes impossible to escape the conclusion that the latter frequently, if not invariably, uses a remedy in proportion to his belief in its efficacy. His very beliefs may colour his observations, as perhaps they did in the case of our patients who described Tofrānil as varying in colour from a beautiful salmon pink to a dirty brown. I fear that I am not one of those who believe that man is objective; rather do I believe that he is intensely subjective, if not even at times frankly procrustean. He sees what he wants to see and ignores what he doesn't want to see. There is no reason to deplore such subjectivity, no reason to contrast subjectivity with objectivity to the detriment of the former, but merely to underline its presence for the purposes of study. Whether such study is always necessary I am not sure — perhaps one should merely be satisfied with one's patients getting better.

From the clinician's point of view, the most widely voiced and, in Bradford Hill's view, "the most foolish criticism of the statistical approach in medicine, is that human beings are too variable to allow

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of the contrast inherent in a controlled trial of a remedy" (2). Thus, he continues that "if each patient is unique there can be nothing for the statistician to count, but, if this is true, it has always seemed to me that the bottom falls out of the clinical approach as well as the statistical. If each patient is unique, how can the basis of treatment be found in the past observations of other patients? In fact, of course, physicians do not act like this; they base their methods of choice upon what they have seen happen before, whether it be in only two or three cases or in a score." Nevertheless, in such a comparison we immediately encounter subjective bias.

To help us in this maze of variability we are forever seeking to establish parameters. In this context, I would wish to speak of only one of the parameters that have been mentioned, not only by Dr. Shepherd, but throughout this meeting, namely the constancy of response of the depressed patient to electroconvulsive therapy. If this becomes our yardstick of measurement against which we assess other treatments, perhaps we should re-examine our criterion. I am well aware that when I suggest that ECT in major depressive illness* may not be the panacea sometimes suggested, I become an iconoclast and risk all the feeling that those who criticize icons arouse. Dr. Freyhan has drawn attention to the conflicting evidence in the literature suggesting that such illness may perhaps be better treated by other methods than shock treatment. I have little reason to doubt Dr. Cook's memories of the wards at Bexley when he first went there. However, I wonder whether memory is always a good substitute for controlled and recorded observation and whether the changes that have occurred may only in part be due to the introduction of physical treatment. Karagulla, in a controversial paper reviewing the admissions to the Royal Edinburgh Hospital for Mental and Nervous Disorders during the years 1900 to 1948, carefully studied 923 patients in 1611 hospital admissions (3). Her most important finding was perhaps that 80-90% of depressed patients recovered or improved and that the proportion who did not improve remained constant between the era when ECT was available and the era when it was not. 61% of these patients had only one admission to hospital for a depressive illness, and a relatively large number of patients required only 6 weeks' stay in hospital. These findings emphasized, in her words, "the high expectation of recovery in depressive states and this in turn underlined the necessity for the application of stringent criteria in the evaluation of any form of therapy which claims to accelerate this process of natural recovery." Her other conclusions, namely that the use of ECT did not shorten the duration of hospital stay, that it did not increase the percentage discharged from hospital, that those who were classified as recovered with ECT showed a somewhat higher tendency toward readmission than those who recovered without ECT, and that the suicide rate was slightly higher in those treated with ECT than in those not treated with ECT, have all been variously criticised, most notably by Slater (4). However, even if these are discounted, her paper still underlines the good prognosis in most hospitalized depressions and the failure of ECT to influence the outcome of those with a bad prognosis. Thus, I wonder how many patients, even with severe illness, would recover, and perhaps in not much longer a time than with ECT, if merely rested in the protective environment of a hospital. I consider that the reason they are not treated in this way lies in the enormous importunity presented by the patients' symptoms and the demands of the relatives for the doctor to produce quick relief. In this way, I would echo Dr. Lehmann's words that the psychiatric tolerance to depressive symptoms in patients has been so much reduced during the last 15 years that many psychiatrists may find it difficult to wait 2-4 weeks before seeing a definite lifting of depression in their patients. Nevertheless, the efficacy of a method of treatment of a disease may be better judged by the long-term results over perhaps a period of 5-10 years than by the immediate improvement, gratifying though it be to the attendant physician. Perhaps harm may be done by attempting an undue shortening of the period of sickness occasioned by depressive illness. Without knowledge of relapse and readmission rates, short hospital stays are meaningless.

Here, however, I consider that Tofranil has a most important role to play. By its sedative action it seems to reduce both the suffering of the patient and perhaps the guilt experienced by psychiatrist and nurse in allowing the patient to bear his illness during the longer period of time required by "spontaneous" remission. In this way, perhaps, the drug can be regarded as a solvent of superego not only in the patient but also in his attendants.

Thus, in conclusion, I would say that if Tofranil played no greater part, and I personally feel sure that it will, than in helping us to re-examine the natural history of major depressive illness, its advent will have been well worth while.

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*Defined empirically as depressive illness in which the majority of psychiatrists would nowadays adjudge the patient suitable for ECT.

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General discussion from the floor (summarized)

The method of approach to the clinical problem which had been discussed at this symposium was criticized by one of the participants. This method might be called the "anecdotal method," consisting of general clinical observation. The need was stressed for other studies of a type characterized by a more explicit statement of purpose and a more pertinent design. Three major approaches were noted: study of the drug effect, exploration of the symptoms and syndromes of a particular disease through a study of the effect of drugs upon them, and statistical studies of the therapeutic effect. It was felt by this discussant that there had been much confusion of these three different research designs during the conference. The need for certain requirements in the so-called "before-after" design was stressed, including: (1) Standards and criteria that provide repeatable observations; (2) Knowledge of other relevant variables in the experimental field and a conceptualization of their relationship with other aspects of the

study; (3) A clear picture of the natural history of the variables under study; (4) Knowledge about the relationship between the population studied and the general population in which the variable as a whole exists. This speaker felt that most papers presented to date had been really preliminary statements.

The efficacy of the therapist's clinical judgment in assessing a patient's progress and thereby providing a control was stressed by several discussants.

Reference was made to the time factor; it was noted that in the New York area electroshock is more commonly used where the length of stay of the patient has more direct economic repercussions upon each individual. It was stressed that in discussing one new approach to the treatment of one disease, there is no implication that one should thereby throw out all other treatments which have previously been proved efficacious. The fact that an increasing number of approaches is available is felt to be an index of progress in psychiatry.

DRUG TREATMENT OF DEPRESSIVE STATES*

P. KIELHOLZ**

The psychopathology and therapy of the depressive states has unfortunately never aroused the same interest as the problems of schizophrenia, so that in the sphere of the affective disturbances there are still many important questions remaining unanswered. Moreover, an examination of the records of all in-patients treated for psychogenic and endogenous depressions from 1920 to 1957 at the Psychiatric Clinic of Basle University has shown that depressive conditions of the

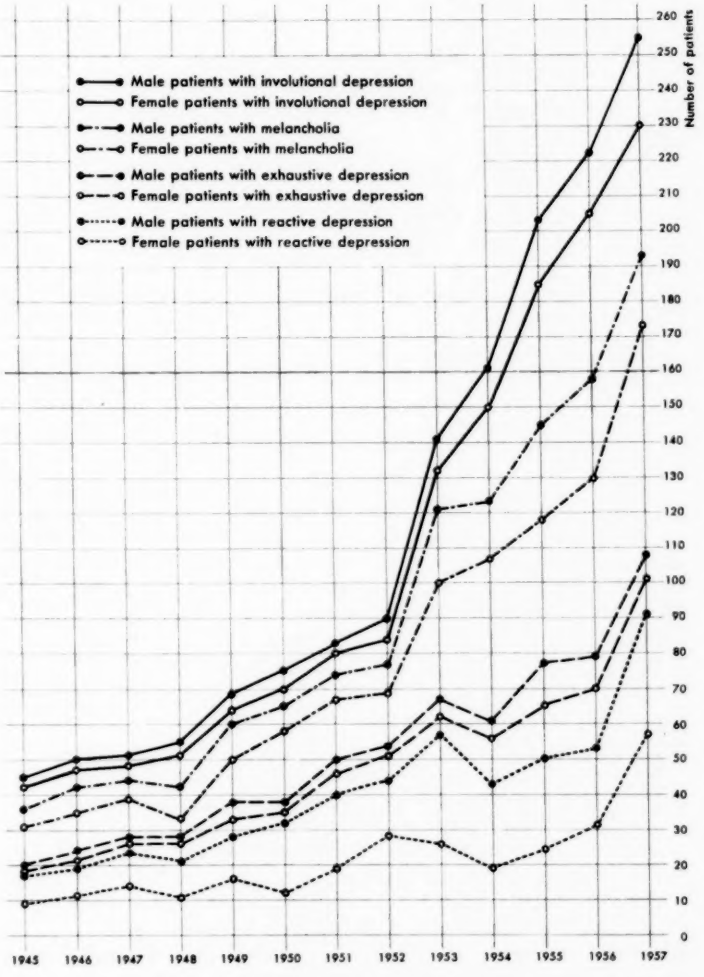

Fig. 1. Graph showing the number of patients with depressive manifestations who were treated from 1945-1957 in our hospital.

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most varied origin have increased notably, especially in recent years. This increase, shown graphically in Figure 1, is no doubt due to a variety of factors associated with modern life. It is particularly marked in respect of female patients with reactive depressions, melancholias and involutional depressions. During the last 10 years the number of depressed patients treated in the clinic has increased more than fivefold, a state of affairs which suggests that our present diagnostic and therapeutic methods should be closely examined.

In Switzerland in recent years exhaustive depressions have been the subject of repeated studies. They are seldom seen in hospital wards since out-patient treatment is often possible. Despite an immense amount of investigation (1-6) no specific physiological or endocrinological changes have yet been observed in the depressive states. In attempting to discover the original cause of a depression we are therefore reduced to drawing conclusions from what the patient regards as the principal reason for the onset of his depression.

Looking at exhaustive depressions from this point of view we see that like all diseases, they are conditioned by the constitution, disposition and circumstances of the patient. As regards character, the predominant personality is sensitive, often somewhat infantile, but often also over-conscientious, with an exaggerated feeling of responsibility, pedantic, ambitious, egocentric, with a tendency to perfectionism. Persons mainly affected are those who become increasingly isolated as a result of their introversion, or who make excessive demands on themselves as a result of their perfectionism and conscientiousness.

The commonest factors starting off a depression are excessive intellectual work of a responsible nature, restlessness, haste and noise, as also the necessity of making hurried decisions, family or professional conflicts, unsatisfying work and ethical or religious conflicts of conscience. The patient is depressed much less by the amount of work he has to do than by adverse environmental influences and affective tensions. From the psychopathological standpoint the course of an exhaustive depression is almost always marked by three phases:

1. The hyperaesthetic-asthenic prodromal phase. Increasing affective and intellectual tension first becomes evident in the form of over-sensitivity, irritability, increased affective reactivity and sleep disturbance which gradually results in a sleep-deficit. Not only are the irritability and lassitude increased but there is also a loss of capacity to concentrate and work, resulting in a feeling of anxious self-disparagement. If the emotional stress increases still further owing to additional adverse environmental stimuli the affective tension is frequently projected via the autonomic nervous system into the somatic sphere, so that the depression enters the second phase.

2. Psychosomatic phase. The transformation is marked mainly by headache, giddiness, precordial apprehension, extra-systoles and digestive disturbances. These somatic disturbances lead to ever more introspection and open the way to hypochondriac fears. From the psychopathological point of view, there is usually a basal mood of gloomy apathy or apprehensive hypochondria, with fatigue, weakness of concentration and affective incontinence. The apprehensive introspection intensifies the emotional pressure, and this in turn reinforces the somatic disturbances, so that a vicious circle is established. This second phase often lasts for years, when an additional psychic stress suddenly transforms it into the third phase, the actual depression.

3. Phase of exhaustive depression. This is usually brought on by minimal additional stresses. These stimuli are the final impulses which intensify the emotional stress and invade the "vital sphere." According to Staehelin (7) and Schneider (8), the "vital sphere" is the sphere of the bodily feelings, drives, instincts

and power of resistance. The result is a depressive state with a basic mood of sadness, oppression or anxiety and an inhibition of the psychic and motor functions.

Out-patient treatment is often possible during the hyperaesthetic-asthenic prodromal phase, neuroplegic drugs being prescribed to relieve the tension and ensure sleep.

In patients with pronounced symptoms of depression an initial trial with Tofrānil* can be made on an out-patient basis. One 25-mg tablet in the morning, at midday and at 4 p.m. is prescribed at the start for a period of 3 days; the dose is then slowly increased according to the reaction of the patient and any side effects which may appear. This cautious increase of dosage is necessary in out-patient treatment since otherwise the patients simply stop taking the drug when side effects appear. Insomnia must, of course, be counteracted with neuroleptics or hypnotics.

Using this regime an improvement in the depression was obtained in 60% of patients. If the depressive state does not improve within 3 weeks, in-patient treatment is to be advised. The dangerous vicious circle of insomnia and vegetative dystonia must be interrupted by an intensive combined therapy with neuroplegics and hypnotics. After this initial phase, lasting 10 days, stabilization can be attained within a few weeks by means of Tofrānil in combination with insulin treatment if the patient's physical condition is poor.

Comparative tests of the effectiveness of antidepressive drugs must be made on depressive states which have diagnostic features as uniform as possible and whose course is well known. The periodic melancholias have proved to be the most suitable for this purpose. Since there are certain differences in different languages regarding the nomenclature of the depressive states, I should like to preface my further remarks with a short definition of periodic melancholia. By this we understand affective deviations appearing periodically, brought on in the main, according to modern conceptions, by constitutional factors, and belonging to the manic-depressive group of disorders.

By comparing untreated and treated depressive phases we have attempted to evaluate the effects of old and new methods of treatment. Here we shall confine ourselves to a diagrammatic presentation of the results. As in all diseases whose pathogenesis is unknown, a great number of drugs have been, and still are, recommended for the treatment of depression. I can, of course, only refer to a few of these.

During the last century opium was recommended for many disorders, including the depressive states. It was known much earlier that opium could exert a beneficial action not only on pain but also on anxiety, internal tension and unrest. Following the introduction of insulin treatment into psychiatry, its use, too, was extended to the depressive states. Comparative phase studies have now shown that both anxiety and unrest in agitated melancholia can be mitigated with the help of opium and insulin; however, no shortening of the duration of the phase can be achieved (Figure 2).

Over the last 20 years opium and insulin treatments have mainly given way to drug convulsive therapy and this in turn to electroshock therapy (ECT), which is simpler to use and easier to control. The figures for remissions obtained in melancholia by means of ECT varied in earlier investigations from 75 to 95%. During recent years these high rates of remission have been increasingly questioned. During the first phase the depression syndrome can certainly be much improved in approximately 40% of patients with 6 to 12 shocks, but in the later phases a distinct remission cannot usually be obtained until 6 to 8 weeks after the onset of the melancholic attack. In Figure 3 it is evident that depressive symptoms

*Trade Mark.

often again become evident 2 to 4 weeks after the treatment has been stopped, that is to say when the patient has already left hospital, and do not completely disappear until the phase abates.

Phase comparison in agitated melancholics under long treatment with opium and with insulin

(Two typical phase courses of each treatment, in 28 and 83 cases respectively)

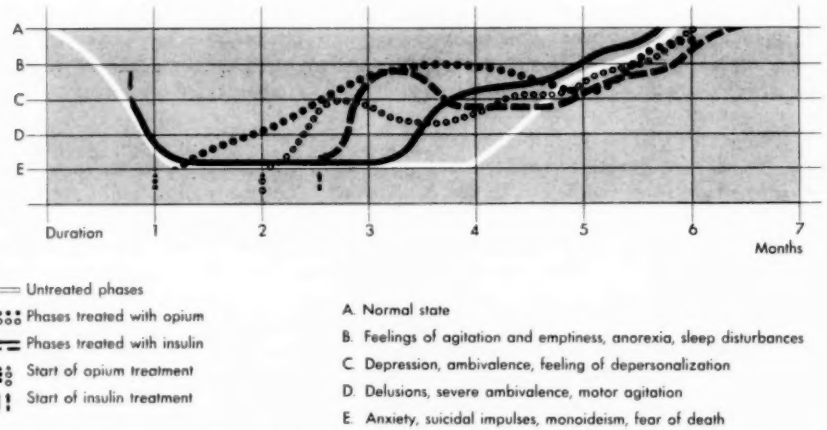

Fig. 2. Investigations comparing the different phases have shown that both anxiety and unrest in agitated melancholia can be mitigated with the help of opium and insulin; however a shortening of the duration of the phase cannot be brought about.

Phase comparison in melancholics under electroshock treatment

(Three typical phase courses, in 86 cases)

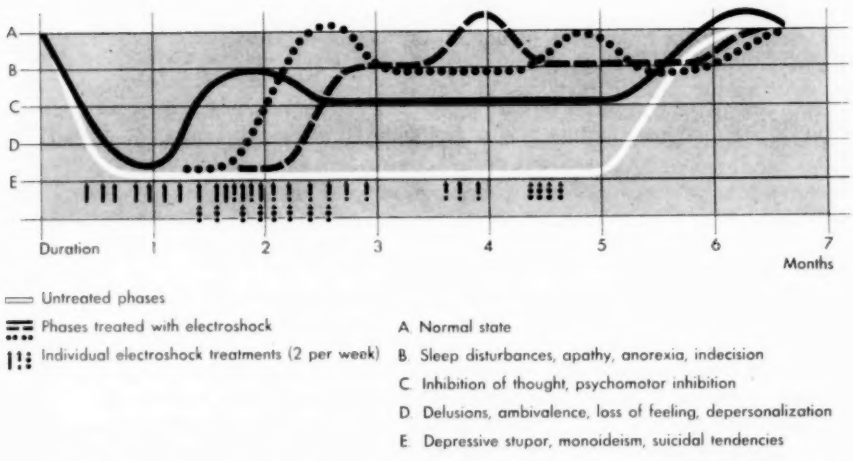

Fig. 3. Two to four weeks after the treatment has stopped, that is at the time when the patients have already left hospital, depressive symptoms often again become evident, and do not completely disappear until the phase abates.

Amphetamine and similar drugs have been publicized as antidepressives, especially since the war. They seem to increase driving power, especially the elementary one of movement, and to relieve feelings of tiredness, but they have little or no action on the basic mood. Amphetamines are therefore contraindicated in endogenous depressive states since in the agitated forms they increase the anxiety and unrest while in retarded melancholias they often lead to internal excitement and sometimes start off severe episodes of fear which increase suicidal tendencies. Moreover, these drugs increase physical weakness by reducing the period of sleep and decreasing the appetite. Following the discovery of the neuroplegics it was hoped that they would have a favourable effect on depressive states. We showed as early as 1953, however, that neuroplegics were indicated only in the types with anxiety and agitation, where they are often quite successful in relieving these symptoms, as shown in Figure 4.

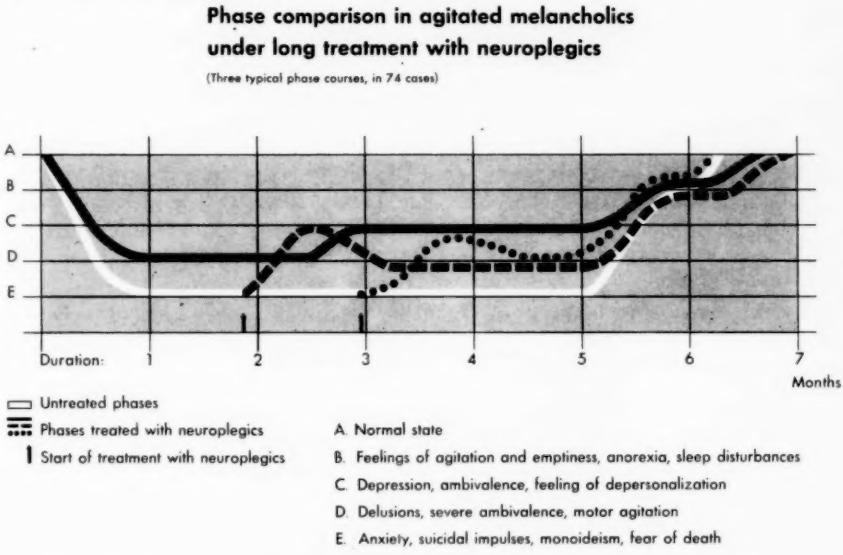

Fig. 4. The anxiety and unrest can often be relieved successfully with neuroplegics. Tension is reduced and tranquillity achieved, so that the patients acquire a certain remoteness from the burden of their depressive fantasies and suicidal impulses. However, the basic depressive mood still persists.

Patients are thus largely freed from the burden of their depressive fantasies and suicidal impulses. However, the basic depressive mood still persists. In patients with retarded melancholia the neuroplegics are even contraindicated, since these drugs deepen the depression still further by their additional effect of reducing the energy level.

Following the neuroplegics iproniazid, an inhibitor of monamine oxidase, was recommended as an antidepressive agent. Iproniazid and its derivatives strengthen driving power to some extent and also increase appetite, thus leading to a general improvement with a corresponding gain in weight. Unfortunately an effective dose over a considerable period sometimes causes such persistent circulatory collapse that the drug must be abandoned.

For two years now we have therefore been attempting to treat melancholic states with Tofrānil. This compound has a selective action on vital depressive states (9-13).

Even with Tofrānil it is not possible to stop the melancholia at the very beginning of the phase. However, in 60% of patients a significant improvement sets in within 3 to 20 days (Figure 5). In half of these patients suppression of the depressive symptoms is even achieved. If the treatment is discontinued before remission of the phase, however, the depressive symptoms reappear. In the remaining 40% of patients the drug effects only a slight improvement or none at all. In those forms which do not respond to Tofrānil therapy an improvement can sometimes be brought about by combining the drug with ECT, or in anxiety-depressive states by combining it with neuroplegics.

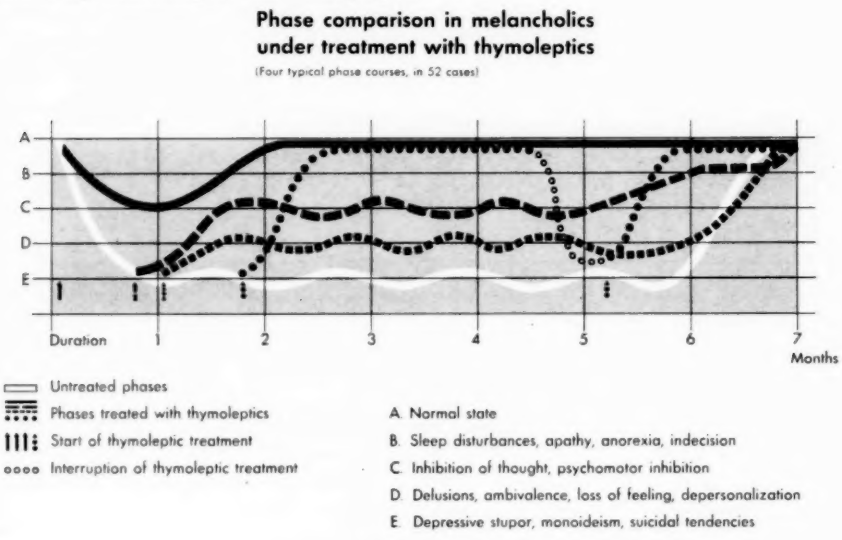

Fig. 5. See text.

Our investigations have shown that depressive phases cannot be cleared up with the means at our disposal at present. All we can do by means of the methods of treatment available at present is to suppress the symptoms of depression in whole or in part. Thus we still do not have available a treatment which permits a causal or specific therapy of melancholia. Nevertheless the recent success of new methods of treatment gives cause for hope that drugs will be discovered which are still more effective.

Résumé

Une nette augmentation des cas de dépression au cours de l'année dernière a nécessité une revision du diagnostic et du traitement de ces affections. Du fait que ce sont principalement des états d'épuisements qui ont été observés, l'auteur esquisse pour commencer le diagnostic de ces manifestations dépressives, et la thérapeutique à leur appliquer. Il indique d'abord la prédominance de certains traits de caractère chez ces patients, pour montrer comment, sur ce terrain prédisposé par sa constitution ou par la névrose, l'état dépressif se développe après des années d'influences extérieures délétères, sur le plan affectif. Au point de vue psychopathologique, trois phases peuvent être distinguées plus ou moins nettement: la première hyperesthésique et asthénique, une autre psychosomatique, qui se distingue surtout par des troubles somatiques psychogènes, enfin une phase dé-

pressive proprement dite, qui survient dans la règle par le surajoutement de chocs psychiques ou corporels de minime importance.

L'auteur indique ensuite le résultat de l'étude comparée des différentes phases, ou cours des mélancolies périodiques. En confrontant, chez les patients, les phases traitées et les phases non traitées, il tente de définir l'efficacité des divers médicaments antidépressifs. Les substances étudiées présentent de nettes différences dans leur activité, en rapport avec l'étiologie et la profondeur de la dépression, ainsi qu'avec l'influence de l'inhibition ou de l'angoisse.

Avec les moyens médicamenteux à disposition jusqu'à maintenant, il n'était pas possible de guérir la phase dépressive, ni de l'abréger. Tout au plus arrivait-on, par une médication continue, à estomper les symptômes. Les neuroleptiques parviennent souvent à diminuer la névrose d'angoisse chez les agités mélancoliques, mais la dépression fondamentale demeure non influencée.

Récemment, Tofrānil, une substance du groupe de l'iminodibenzyle, nous a mis en mesure d'exercer une influence sur cette base pathologique, et par là de faire disparaître complètement la symptomatologie dépressive chez une partie des sujets atteints de mélancolie. La question demeure encore ouverte, de savoir si elle parvient à prolonger les intervalles libres ou à mettre le malade complètement à l'abri des rechutes. Sur la base de ses recherches, l'auteur pencherait plutôt pour la négative.

L'étude comparative des différentes phases indique que les remèdes actuels ne nous permettent pas encore d'effectuer un traitement causal ou spécifique de la mélancolie. Cependant, les succès thérapeutiques récents permettent d'espérer que des substances encore plus actives seront découvertes dans un proche avenir.

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Discussion

FRANK J. AYD, JR.*

The role of chemistry in psychiatry is amply demonstrated by a new era of pharmacotherapy ushered in by the phenothiazine and rauwolfia derivatives. These compounds and the more recent anti-depressants indicate how chemical manipulations performed in the laboratory can influence mental health and even change psychiatric practice.

Structurally, Tofrānil, an iminodibenzyl derivative, may be compared to the phenothiazine derivative promazine from which it differs by the substitution of a 2-carbon chain for the sulfur atom in the ring system. On this basis it could be postulated that Tofrānil would probably be a weak tranquilizer with a propensity to produce certain autonomic, dermatologic, systemic and neurologic side effects similar to those caused by promazine. In the clinic this has been so with the major exception that Tofrānil is not a tranquilizer, but instead a specific anti-depressant, as Dr. Kielholz's report indicates. As an anti-depressant, Tofrānil is also unique since clinically it differs markedly from other anti-depressants, especially the amine oxidase inhibitors.

My clinical experience with Tofrānil parallels that of Dr. Kielholz. In the past year my associates and I have prescribed this drug for 150 patients diagnostically classified: manic-depressive, depressed,

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involutional depression, schizophrenic reaction with depressive features, and neurotic and reactive depressions. These patients were chosen for Tofrānil therapy primarily because depressed mood, psychomotor retardation, feelings of guilt, hopelessness or despair, insomnia, anorexia, or functional somatic complaints were their predominant symptoms. All patients were treated in a general hospital or on an ambulatory basis.

The initial dose of Tofrānil was 25 or 50 mg orally or parenterally three times a day. If necessary, the dosage was increased by increments of 25 mg until improvement occurred or toxic side effects interfered. As a rule small doses were given frequently rather than large doses infrequently. Although the daily dose ranged from 75 to 300 mg the most effective dose was 75 to 150 mg a day.

Dr. Kielholz stated that if Tofrānil is stopped before the remission phase the depressive symptoms appear again. We have found that Tofrānil must be discontinued gradually over a period of several months. In a few instances symptoms recurred as the dose was reduced. In some cases symptoms disappeared on resumption of Tofrānil; in others, symptoms did not disappear, being instead resistant to further Tofrānil therapy. This latter clinical phenomenon occurred most often in those patients with chronic depressions.

In addition to Tofrānil, all patients with insomnia were given an hypnotic at night. Anxious patients and those with schizophrenic features were treated with a combination of Tofrānil and a tranquilizer, either thiopropazate, perphenazine, or trifluoperazine. This combined medication was necessary, practical and safe. Because of the frequency of weakness and dizziness in the first weeks of treatment methylphenidate 10 to 20 mg once or twice a day was added whenever these side effects appeared.

This technique of therapy resulted in 25% complete remissions, 48% partial remissions and 27% failures. The majority of the improved patients showed an onset of symptomatic relief within 3 to 7 days, although at least two weeks were needed before genuine clinical improvement was evident. If a patient had not shown much change after six weeks on Tofrānil it was unlikely that he would benefit from further therapy. The most favorable therapeutic results were in those patients taking 75 to 150 mg a day. To exceed 200 mg a day, especially in patients over 65, with the hope of increasing the therapeutic effectiveness of Tofrānil was usually futile. Quite a few patients were made clinically worse with the higher doses. In addition to an increase of autonomic side effects there was a risk of neurologic (tremors, convulsions), cardiovascular (tachycardia, syncope or hypotension, dyspnea) and psychiatric reactions.

Dr. Kielholz made no mention of the side effects of Tofrānil, which in my opinion merit consideration. This drug caused weakness and fatigue, drowsiness, dizziness, dryness of the mouth, blurred vision, nausea, vomiting and diarrhea, constipation, sweating (predominantly of the upper half of the body), tachycardia, collapse (especially in elderly patients), convulsions, skin eruptions, and bladder retention. It should be noted that similar side effects are frequently seen with promazine and mepazine. The tachycardia indicates that this drug should be prescribed cautiously to patients with known cardiac disease. Some of our patients had pulse rates as high as 140. This could account for the several cases of coronary occlusion reported at this meeting.

Tofrānil also affected the blood picture. In our series we encountered leucopenia and leucocytosis but no eosinophilia. Since this drug structurally is close to promazine and has many of the side effects of promazine, it is possible that Tofrānil may cause agranulocytosis. Although we have not had jaundice, several cases have been reported at this conference. It appears to occur in about 1% of cases.

Side effects were most common in the early weeks of treatment when higher doses are the rule. They also occurred most often in older patients. Most side effects disappeared as the dosage of Tofrānil was lowered. Apparently, the more side effects in a particular patient the poorer the therapeutic result.

Dr. Kielholz is to be commended for his astute observations regarding the clinical effectiveness of Tofrānil in depressive states. His observations that this drug merely suppresses or controls depressive symptoms until the end of the depressive cycle are most apt.

General discussion from the floor (summarized)

Considerable discussion ensued on the indications for Tofrānil, and treatment groups were distinguished by one speaker as follows: (1) In the neurotic depression psychotherapy should be used; (2) In simple, mild to moderate endogenous depression Tofrānil is indicated; (3) In severe depression, with agitation and the possibility of paranoid formation, electroconvulsive therapy is indicated; (4) In recurrent endogenous depression the preventive electroconvulsive therapy technique should be used, i.e. a five-year plan of electroshock therapy as follows — one per month for three years, once every two months during the fourth year, and once every three or four months during the fifth and final year. This discussant also brought up another treatment possibility, i.e. the combination of sleep and electroshock therapy for certain recurrent cases of depression with marked anxiety.

The use of Tofrānil to prevent relapses in recurrent depressions was pointed out by another psychiatrist. A later speaker questioned the efficacy of the five-year follow-up electrotherapy treatment plan, inasmuch as it is widely known that this type of patient is often not at all keen to receive follow-up therapy. It was felt by this speaker that the patient who carried on with the five-year plan may have a certain grouping of psychological factors which might make an interesting study in themselves, and might allow one to determine whether these data apply only to those individuals and not to others. In answer it was stressed that a very intensive follow-up plan was used to keep contact with patients, and further that special precautions were taken to make the procedure itself less anxiety-provoking.

Although Dr. Kielholz felt that the depression must run its course and that drugs or ECT only suppress the depression and do not exert a curative effect on it, other participants believed that both ECT and Tofrānil tend to have a predictably good effect without a return of depression. Dr. Kielholz's position was supported by another discussant who noted the existence of phasic depressions which last six months or so and then get better.

A third speaker felt that Tofrānil could improve chronic or long-standing depressions with reasonable assurance that no relapse would occur.

Dr. Kielholz then replied that the patient always becomes interested in his treatment and that the interest varies according to the particular treatment given. This, he feels, is a factor in the success of the treatment involved.

He said he could not confirm the results of other investigators in reference to the use of Tofrānil for periodic melancholia. He urged that it is wise to reduce the dosage of Tofrānil gradually and progressively until a stopping point is reached.

In regard to convulsions, it was his feeling that the convulsions seen perhaps represented latent epilepsy. Only at the beginning of treatment had Dr. Kielholz observed the collapse phenomena that had been mentioned.

ORGANIC (NON-DRUG) THERAPY OF DEPRESSION

LOTHAR B. KALINOWSKY*

A discussion of somatic treatments in depressions not including pharmacotherapy cannot entirely ignore the newer drugs because their introduction has greatly modified the indications for the previous somatic treatments. However, the hope that pharmacotherapy would do away completely with the strangely unpopular shock treatments and surgical methods was premature. It soon became obvious that the neuroplegic drugs or "tranquilizers" changed little in the treatment of depressions. A real change in the application of the older treatments, especially electroconvulsive therapy (ECT) may occur as a consequence of the introduction of antidepressant drugs. Yet thus far the application of convulsive therapy as the quickest and most reliable way to remove severe depressive syndromes is still widely used. The need for electroconvulsive therapy, however, varies with different types of depressive syndromes, and it will be necessary to discuss groups of depressive patients and their response to treatments separately in order to come to a conclusion as to which of the available treatments should be given preference in an individual patient at a given stage of his illness. The first and larger part of the discussion will deal with the results of ECT; a shorter discussion of psychosurgery and some other methods will follow.

It is known that convulsive therapy was introduced by Meduna for schizophrenia without a thought of what later became its most extensive area of application. The theory that schizophrenia and epilepsy exclude each other, and some clinical observations on the removal of psychotic syndromes, led to the discovery of convulsive therapy, and it was not until several years later that its usefulness in depressions was recognized. This is not the place to discuss technical problems of convulsive therapy. This presentation will primarily deal with the electric form of convulsive therapy. Pharmacological convulsive therapy with pentamethylenetetrazol has not entirely been abandoned, and has even found a revival in certain schizophrenic conditions where it seems to be slightly superior to ECT; but this superiority has never been claimed for depressions. A newer modification of convulsive therapy, the induction of convulsions by means of the inhalant "Indoklon" offers interesting possibilities, but its indications do not differ from those of other types of convulsive therapy. It is, therefore, justified to limit the discussion of convulsive therapy of depressions to ECT.

The various affective psychoses or endogenous depressive states respond equally well to ECT. The claim for a specific effect of any treatment in psychiatry is usually avoided, but nothing comes closer to a specific effect than the response of a typical depression to a predictable number of three or four electric shock treatments. It is the accepted procedure to give a few additional treatments to prevent a relapse, but it is hardly necessary to give more than six or eight treatments in the majority of cases, and results of close to 90 to 100 per cent have been reported by some workers when they limited their statistics to pure cases of affective psychoses. The rare occurrence of relapses is quite contrary to what we see in depressive syndromes of schizophrenia and some other psychotic syndromes associated with depression, as will be discussed later. The effect of ECT is limited to the depressive episode as such and does not influence in any way the course of the illness as, for example, the occurrence of future episodes.

This is particularly true for the first group of depressions we are dealing with, the depressive phase of a manic-depressive psychosis. If these patients are treated

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with ECT depressive episodes occur as often as they would without ECT. It will be discussed later in more detail that the shifting from a depressive to a manic episode which occurs after spontaneous remissions is also seen after ECT remissions. It is surprising that this is not prevented by ECT in spite of the fact that the manic phase also can be treated successfully with convulsive methods, although treatment has to be more intense. Long-term follow-ups do not show any difference between ECT-treated and untreated depressions of a manic-depressive patient. Yet the possibility of shortening a depressive episode at will and the removal of the great suicidal risk are forceful arguments in favor of ECT. Also it must not be overlooked that the suicidal risk is more severe in the beginning of a depression than in the clearing-up phase. It is an old clinical experience that during the height of a depression when the patient is severely retarded and deprived of all his initiative, including self-destructive impulses, suicides are rare. This must be considered in weighing the decision between ECT and antidepressant drugs. It will depend on the clinical judgment of the therapist how seriously he considers the patient threatened by suicide. While I myself consider Tofrānil* an extremely valuable addition to our therapeutic armamentarium, the suicidal risk frequently swings my decision toward immediate ECT. Social aspects such as the quicker and more reliable response of depressions to ECT also work in favor of a greater application of ECT than would be expected after the introduction of various antidepressant drugs.

Acquaintance with the work in hospitals, particularly psychiatric wards in general hospitals, reveals that in this type of psychiatric facility drugs are not given much of a chance because of financial considerations. The predictability of the time required for the five or six electric shock treatments necessary in a depression, and on the other hand the uncertainty of the response to drugs, make it difficult to submit a patient who must pay for his hospital stay to pharmacotherapy which in many cases must still be followed by ECT. Perhaps this is not justified in view of the relatively quick response to Tofrānil when it works at all. There is some evidence that the number of ECT's can be reduced after pharmacotherapy. W. Schmitt showed that as few as one or two convulsive treatments after an unconvincing result with Tofrānil alone could lead to the desired therapeutic effect. ECT was usually given only after three to six weeks of medication. Such experiences diminish the hope that ECT can be given up as the best predictable treatment in all depressions. ECT clears up agitated and retarded depressions alike, whereas the effect of Tofrānil seems to be limited to the non-agitated type of depression. The simultaneous treatment with Tofrānil and ECT, which we ourselves were reluctant to use so far, has been applied by an increasing number of psychiatrists without untoward side effects or complications. We doubt, however, whether a reduction in the number of ECT's would justify a prolongation of the total treatment time of a depression. However, we do make increasing use of Tofrānil after the actual symptoms of a depression begin to disappear, which is usually the case after three or four treatments. In patients who have a tendency to an early relapse, as is particularly true for some atypical depressions, we follow up ECT with Tofrānil, and in this way reduce the rather large number of shock treatments necessary in such patients. A few patients who had been observed during previous depressions, and in a new depression were treated unsuccessfully with Tofrānil, recovered with a smaller number of electric shock treatments than during their preceding episodes.

There seems to be a basic difference in the way pharmacotherapy and ECT work in depressions. Many workers who are using Tofrānil, including myself, found that most patients responding to Tofrānil after a few days must be kept under this medication for a considerable length of time. In some patients with a history of

*Trade Mark.

previous untreated depressions of known duration, it appears that medication with Tofrānil is necessary almost as long as the depression usually lasted in these particular patients. This would mean that Tofrānil lifts the depressive mood in a purely symptomatic fashion, while ECT removes the depression radically as far as the individual episode is concerned. If these observations are confirmed they would favor a continuation of ECT as the treatment of choice in the more serious depressions.

It is obviously not right to call the effect of ECT in depressions simply symptomatic. Neither can it be proven that it is a specific treatment of the cause of the illness. We agree with Von Baeyer that we must distinguish between a therapeutic effect tied to the time of the treatment and one which lasts beyond the actual treatment. Depressions and other psychoses can disappear temporarily for the duration of the organic changes caused by the convulsive treatments. Electroencephalographic changes can last for one or several weeks, and may persist even when the psychopathological changes of confusion or memory impairment are no longer noticeable. They are expressions of an effect on the brain, and the question arises whether this brain disturbance suppresses the psychotic syndrome of depression or other disorder. An improvement limited more or less to this period of disturbed brain function is quite similar to the effect of a drug which covers up symptoms as long as the blood level of the drug is high enough, but does not act beyond this period. If, however, as is the case in the majority of depressions treated with ECT, the therapeutic effect remains beyond the period of disturbed brain function (in other words, longer than the effect of shock treatment in a non-depressive, healthy individual) we are justified in speaking of a specific or curative effect of electroconvulsive therapy.

Another question that needs clarification is whether a depression as a psychopathological manifestation requires psychotherapy to avoid recurrence after discontinuation of shock therapy. Statements have been made frequently that psychotherapy is indispensable, but these can be easily disproven. It has been said already that amnesia, in the sense of forgetting the experiences which presumably led to the depression, cannot serve as an explanation for the shock effect. Neither can it be said that ECT works in the same way as Klaesi's sleep treatment or the older opium treatment in depressions. These methods could be explained as means to give the patient complete emotional rest, and in a certain way to give him a new start. This rest could also be a factor in the treatment with neuroplegic drugs and their explanation as hibernation treatment. This rest, also stressed in the Pavlovian concepts of Russian psychiatry, is certainly not present in ECT. Moreover, ECT cannot be called a form of psychotherapy, and the need for psychotherapy after ECT is also unproven.

Another point of both theoretical and practical importance is to what extent manic episodes do not simply follow, but are actually elicited by, the various treatment procedures. ECT very frequently leads to a slight hypomanic state immediately after the treatment. This is of little practical importance and can be interpreted as a short-lasting organic reaction due to the ECT rather than a manic phase of the manic-depressive psychosis. True manic episodes immediately following ECT are extremely rare in my observation. Contrary to this, medication with iproniazid produced manic episodes more often. Such observations have already been reported for Tofrānil too, but they seem to be less frequent than they were with iproniazid. Their occurrence must be taken into consideration when discussing means to prevent future depressive episodes. It is known that since the work of Geoghegan and Stevenson in Canada, preventive ECT for recurrent depressions has become a widely accepted procedure. It is likewise effective in preventing the manic as well as the depressive episodes of a manic-depressive patient. Such monthly and later

bimonthly treatments, also recommended by Cameron, will be reserved for patients with very frequent episodes. While an acute manic episode responds less readily to ECT than a depression, and therefore will nowadays be treated particularly in hospitalized patients with neuroplegic drugs, the preventive value of ECT for manic episodes is at least as successful as that for depressions. In our experience such preventive ECT in manic-depressive patients could not yet be replaced by pharmacotherapy, because neuroplegic drugs after a manic episode often have a depressive effect, and the danger of manic reactions under antidepressant drugs diminishes the preventive value of these drugs after a depressive episode. In any event it is difficult to decide which of the two pharmacotherapeutic groups of drugs should be applied as a means of prevention in a patient tending to both depressive and manic reactions.

The response to ECT is of great interest in the question whether there is a difference between cyclothymic and reactive depressions. Our experience supports the view that many so-called reactive or neurotic depressions are actually cyclothymic depressions in the sense of the affective psychoses, but occurring in patients who also have certain neurotic features. There is a minority of such patients in whom depressive symptoms occur only as a response to adverse circumstances. They do not show the loss of weight seen so regularly in psychotic depressions, and also the sleep disturbances are less pronounced than they are in endogenous depressions. These patients have more often difficulty in falling asleep, while psychotic depressive patients, if they sleep at all, are more apt to wake up early. The poor response to ECT of this latter group of true reactive depressions may be of diagnostic significance and of some importance for the differentiation of depressions in general.

The favorable results of ECT are equally convincing in involutional melancholia, which is probably not a different type of sickness but the same affective psychosis occurring in a certain age group. The immediate response to ECT is an even more important factor in this group, because involutional depressions can persist much longer than manic-depressive depressions. As in all somatic treatments in psychiatry we only support the natural healing tendencies of the organism, but the value of the treatment is well illustrated by the observation that an involutional melancholia, though it may have lasted already a year or two, can be cured by electroshock with the same number of treatments (six or eight) as any short-lasting depression.

Before we speak about the failures in the two groups discussed so far, it may be mentioned that old-age depressions have the same chance of recovering under ECT as depressions in the other age groups. Many workers reported on the reliable and innocuous applicability of ECT in old-age depressions, and particularly reports by Roth and other English workers showed how many psychoses of old age are actually functional psychoses wrongly diagnosed as senile dementia. In such patients careful anamnesis often reveals one or two previous depressions many decades prior to the old-age depression.

So far the picture has been most favorable regarding the response to ECT in typical depressions. This must be followed by a detailed discussion of failures. The present era of the new antidepressant drugs makes this imperative. My personal experience with the first antidepressant drug iproniazid was that this drug was more helpful in the type of depression not responding to ECT than in uncomplicated affective psychoses.

Although I no longer use iproniazid because of the serious liver complications, I was impressed by the fact that a number of chronic and atypical depressions, in which ECT had never helped for more than a few weeks, responded very well to iproniazid. Even though some of these patients tended to become manic, these

manic symptoms could be counteracted by neuroplegic drugs. The superiority of pharmacotherapy over ECT in some of these atypical depressions is undeniable. I have no personal opinion yet as to what extent Tofrānil has the same value in those depressions refractory to ECT. This question must be further clarified on the basis of more psychopathological reports on individual cases if we want to come to a clearer understanding as to when pharmacotherapy is indicated and when ECT.

Depression is a frequent symptom in schizophrenia, and it is therefore not surprising that particularly in younger patients a depressive syndrome is often the predominant symptom of an underlying schizophrenic psychosis. This is best demonstrated by experiences we all have that when a patient with a moderate depression without deep affect is subjected to ECT, he develops a fullblown hallucinatory picture after the first treatment. It is obvious that such a syndrome after the first treatment is not an organic reaction to ECT but the appearance of a real schizophrenic psychosis whose depressive overlay was removed by one electrically induced convulsion. This observation led Halpern to the formulation that ECT may be an aid in the diagnosis of schizophrenia. It also happens most frequently that schizophrenic patients in whom a depression without deep affect seems to be the only symptom respond to a few electric shock treatments but relapse within a week after discontinuation of treatment, an occurrence so often seen in all types of schizophrenics. Further observation of such patients, whose first diagnosis is frequently manic-depressive psychosis, reveals very often that their depression was actually the first symptom of a schizophrenic psychosis and their prognosis was quite different from the favorable outlook in a manic-depressive psychosis. It is in these schizophrenic depressions that insulin coma treatment, possibly combined with some convulsive therapy, is most effective, and it has not been shown convincingly that pharmacotherapy can replace the shock treatments in these cases.

Post-partum depressions fall into this category of depressions with a shallower depressive affect and correspondingly less convincing response to ECT. While they do not have the ominous prognosis of many schizophrenic psychoses beginning with a depression, they have a clear tendency to relapse, and it is here that I find the use of Tofrānil especially valuable in the prevention of relapse after a certain number of ECT's.

Failures with ECT hardly occur in typical cases of involutional melancholia. They are all the more frequent, however, in patients whose depression is complicated by other symptoms such as somatic delusions and hypochondriasis, and the same poor response to ECT is often seen in involutional depressions associated with paranoid symptoms. These cases of involutional psychosis which are not of purely paranoid type but are classified as mixed type are obviously schizophrenic psychoses occurring at a later age. They need much more extensive convulsive therapy and have a considerably less favorable prognosis even with such intensive treatment than cases of involutional melancholia. In these cases regressive ECT or the combination of sleep treatment and regressive ECT, as described by Cameron and Pende in chronic paranoid schizophrenics, should be promising. There is no reason to believe that the older age of these patients prevents them from receiving this combined sleep-regressive shock treatment. Regressive shock therapy with several treatments a day but not associated with sleep treatment has been applied by me in many such cases with results that were superior to regular ECT. This includes a number of patients in whom pharmacotherapy had been tried because of previous failure with regular ECT.

This is the place to discuss a type of chronic depression that occurs in middle age or later and which was not recognized in the psychiatric literature until the introduction of ECT. Every psychiatrist experienced in this treatment is appalled by the resistance of these chronic depressions to ECT. Patients never fail to respond

to a few treatments but they rarely reach a complete freedom from symptoms. If their recovery is incomplete it is only a question of time until the same depressive symptoms recur, and the patient must be treated again. There is reason to believe that these patients have late schizophrenia rather than affective psychoses. I still find it indicated to try ECT in these cases but I immediately place them under Tofrānil if they are known to have a tendency to relapse. Follow-up of patients in this group is too short to draw conclusions, and in some of these cases I had to apply ECT again in spite of medication with Tofrānil.

Depression as a symptom of certain organic diseases of the central nervous system is not rare. In general paresis, depressive mood was more frequent than the much-quoted manic symptomatology. Such depressions cleared up under ECT, and this often made the etiological treatment of the disease by means of penicillin or malaria possible in a general hospital where otherwise such patients could not be kept. In arteriosclerotic or, less frequently, senile brain disease depressive symptoms may also occur, and these respond well to ECT. Here ECT is replaced by antidepressant drugs because the depressive affect or organic basis is usually not very deep, or the arteriosclerotic or senile patient may be simply depressed because he realizes his general decline. Depressed mood in epileptics either as a paroxysmal or a more lasting mood disturbance may be occasionally an indication for one or more convulsive treatments. Brain tumors have been sometimes overlooked, when a patient with previous depressions reacted to the cerebral pathology again with a depressive symptomatology. ECT is contraindicated in such patients, while Tofrānil might have a good symptomatic effect. Experience shows that the symptom of depression responds equally well in organic and functional depressions to present-day treatments, but more material must be gathered before the question of pharmacotherapy versus ECT can be settled in this group.

The other organic, non-drug treatments have found very little application in depressions. It has always been taken for granted that insulin coma treatment is not indicated in depressions. There is some evidence that this is not quite correct, but in the beginning of the insulin era schizophrenia was considered the only indication for this treatment, and later convulsive therapy as a much shorter and less expensive therapy turned out to be a spectacular success in depressions. Some workers who tried insulin had fair results but it never became widely used. Many other treatment procedures were only introduced to be discarded again for one reason or another. Only carbon dioxide treatment has been tried more extensively for a while. Its realm was various neurotic syndromes, and although depressive symptoms in such patients were secondary, they improved in some instances together with the neurotic symptoms.

Some comments are in order regarding psychosurgery in connection with depressions. Frontal lobe surgery, unfortunately discarded prematurely after the introduction of the neuroplegic drugs, is again being considered an important tool in psychiatric therapy but underwent considerable changes in its indications. In schizophrenia the emphasis shifted more and more from chronic deteriorated patients to those non-deteriorating schizophrenics with primarily paranoid or pseudoneurotic symptomatology often associated with depression. Pure depressions in the sense of the affective psychoses were not considered an indication for such surgical procedure. Contrary to Walter Freeman, who preferred lobotomy especially in its transorbital modification to repeated series of ECT, most psychiatrists felt that ECT, even if it must be repeated quite often, does not have any permanent side effects, while frontal lobe surgery often has. Another significant argument against psychosurgery was the observation that the deep depressive affect which characterizes psychotic depressions is the one emotional condition that is not influenced by frontal lobe surgery. While it is obvious that patients lacking emo-

tional response — for example hebephrenics — cannot benefit from psychosurgery, it is less clear why patients with the severest emotional suffering, as represented by depressions, should not have the same benefit as many other groups of patients whose suffering, whether caused by physical or emotional sickness, was greatly relieved by surgical reduction of fronto-thalamic pathways. Contrary to other aggressive behavior, self-destructive tendencies remained unaltered and the literature shows a number of suicides committed in spite of frontal lobe surgery. More recent reports, however, seem to indicate that certain depressions may be an indication for psychosurgery. Recent follow-ups in England, either published or to be published, show convincingly what some of us have seen also in individual cases, namely that patients with chronic depressions may be excellent candidates for psychosurgery. This concerns mainly those chronic depressions of the older age group in whom somatic delusions, hypochondriacal symptoms and other atypical features accompany a depression, and where ECT has only a temporary and unconvincing therapeutic effect, or none at all. It seems that in these patients the basic symptoms are those we are inclined to consider a secondary admixture to the depression, but which are probably the primary symptoms on which some depression is superimposed. In this group pharmacotherapy will be tried but is often not the answer because too many different symptoms occur requiring different medication, and also because these patients are often quite sensitive to side effects of the drugs, and side effects are particularly disturbing to them.

Our own experience is mostly limited to operations in this type of patient with a mixed symptomatology which includes depression. The recent English reports by McKissock, Partridge and Elithorn show that typical depressions respond equally well. Elithorn even found, against our expectations, that endogenous depressions seem to respond more convincingly than reactive depressions. This conclusion was based not only on the impression of the investigator but also on statements the patient himself made when asked whether he was glad or whether he regretted having had the operation. Of the patients with endogenous depressions, 84 per cent answered that they were glad to have had the operation.

A group of patients in whom depression can be a very troublesome symptom for long stretches is represented by pseudoneurotic schizophrenics, who have been shown by Hoch and his co-workers to be particularly good candidates for psychosurgery. The basic symptom of these patients is pan-anxiety, and the psychodynamics of their superimposed depressions are not quite clear. Considerable experience with psychosurgery in these patients shows that once their basic symptoms are removed, the temporary depressive reactions no longer occur. It has been mentioned before that ECT can easily remove the depressive overlay in these pseudo-neurotic schizophrenics, but it never touches the main symptomatology in any lasting way.

The various comments made on the somatic treatments in depressions show how difficult and yet how significant the proper indications for the various treatments have become in recent years. They also show to what extent the psychopathology of an individual case must be studied before the therapist can arrive at the proper decision as to which of the various treatments available to us today is indicated. I resist the temptation to speculate how far the varying therapeutic response of different types of depressions to different treatments increases our understanding of the psychopathology of depressions. It is true that our hopes of coming to a better understanding of psychopathology through our growing ability to influence psychopathological phenomena at will remain unfulfilled. However, the material presenting itself to those interested in the observation of individual cases rather than of large groups of patients is so ample that it must some day improve our understanding of the diseases and symptoms we are treating. This is one goal

that should never be lost sight of in our therapeutic work. The most important practical conclusion which, I hope, will be drawn from this report is that all treatments introduced during the last few decades maintain their value, and that none of them can be replaced entirely by any of the subsequent discoveries in psychiatric therapy.

Résumé

Un exposé sûr les traitements somatiques de la dépression qui exclut la pharmacothérapie, ne peut cependant pas passer totalement sous silence les médicaments récents, car leur introduction a transformé et limité les indications des autres méthodes. Tant que nous n'avons eu à disposition que des substances neuroplégiques, ou "tranquillisants", nos espoirs d'en finir avec les traitements par le choc, extrêmement impopulaires, ou avec les méthodes chirurgicales, se sont montrés prématurés. C'était le cas en particulier pour ce qui concerne le syndrome dépressif. L'entrée en scène des médicaments antidépressifs a eu pour conséquence de modifier les applications des anciens procédés, en particulier de l'électrochoc. Actuellement encore ce dernier, en tant que méthode la plus sûre et la plus rapide de traitement des syndromes dépressifs graves, est le moyen le plus généralement employé. L'efficacité de cette thérapeutique, ainsi que la confiance qu'elle inspire, varient cependant avec les divers types de dépression. L'auteur traite en particulier des diverses catégories de patients. La première partie de son travail, et la plus étendue, concerne les indications et les résultats de l'électrochoc. Un exposé plus bref concerne la psychochirurgie et quelques autres méthodes.

Dans les psychoses dépressives, le danger de suicide constitue l'indication la plus impérative pour l'institution immédiate d'un électrochoc. Les résultats en sont aussi sûrs dans les dépressions maniaco-dépressives ou involutives (qu'elles soient accompagnées d'inhibition ou d'agitation), que dans les dépressions séniles. Ils sont presque aussi favorables dans bon nombre de dépressions psychoréactives ou psychonévrotiques, celles-ci étant souvent des psychoses affectives accélérées par un stress émotif ou survenant chez des patients porteurs d'une névrose préexistante, mais non apparentée.

Les résultats de l'électrochoc sont beaucoup moins convaincants dans les syndromes dépressifs accompagnant les psychoses schizophréniques et dans les psychoses involutives comportant un mélange de symptômes dépressifs et paranoïdes. De même, les syndromes dépressifs des psychoses organiques sont susceptibles de réagir à l'électrochoc, mais à des degrés divers. Les dépressions chroniques qui débutent à la période involutive et qui sont caractérisées par une atteinte dépressive plus superficielle, ainsi que par des idées de ressentiment plutôt que d'auto-accusation, de l'hypocondrie et d'autres symptômes atypiques, semblent former un groupe à part. Ces patients réagissent à l'électrochoc, mais temporairement et sans effet durable. L'entière disparition des symptômes, si frappante dans d'autres dépressions, n'a pas lieu chez eux, et le malade voit son état empirer à nouveau progressivement après un certain laps de temps. C'est dans ce groupe qu'il y a lieu d'essayer la thérapeutique médicamenteuse, et cela d'autant plus que ces sujets présentent moins de risques au point de vue du suicide.

Quelques remarques de l'auteur concernent les syndromes dépressifs au cours d'affections organiques du système nerveux. La psychochirurgie est examinée sous l'angle de sa capacité d'améliorer une dépression grave, et des cas de suicide malgré cette intervention sont rapportés. Cependant les psychoses chroniques de l'âge avancé demeurent parmi les meilleures indications pour le traitement chirurgical. L'auteur mentionne enfin quelques autres traitements organiques des états dépressifs.

Discussion*

GEORGES SCHNEIDER**

Calling on his long experience in the field of therapy, Dr. Kalinowsky has drawn for us a clear picture of what physical treatments may achieve, but he has been equally eloquent as to their limitations. Not contenting himself with setting forth the historical merits of electro-shock therapy (ECT), he has reviewed the whole problem of indications in the light of recently discovered therapeutic methods. He certainly deserves our congratulations for having kept an open mind while resisting the attraction of novelty and taking great care to state the reasons for his preferences.

The main arguments presented by Dr. Kalinowsky concern electroplexy. To his mind this method appears to be the most reliable and above all the swiftest means by which to treat simple depressive states, whether of the manic-depressive, cyclothymic, involutional, arteriosclerotic or senile type. ECT fails more often in complex or long-lasting affective psychoses, an indication that they fall within the framework of schizophrenias. In respect of the former category, Dr. Kalinowsky claims that ECT has a specific effect. For the latter category, its action is simply symptomatic; once the depressive affect has been overcome, the elements of the basic syndrome become perceptible.

After listening to those speakers who reported on their experience with Tofrānil, I am impressed by the fact that the list of their successes and their failures has very much the same order as with ECT. At the head of the list we always find pure endogenous depressions in which the whole psychopathologic symptomatology has its origin in a disturbance of mood.

Dr. Kalinowsky's preference goes to electroplexy because of its capacity to check the development of the depressive attack in the least possible time. What seems important here is to know whether the speaker has not observed just as rapid an effect with Tofrānil. He admits that this drug may bring about a mood reversal towards hypomania, as does a series of electroshocks. We ourselves have certainly recorded results of this sort. Yet Dr. Kalinowsky suggests that the action of Tofrānil is purely symptomatic, on the grounds that a maintenance dosage is required for a period at least as long as that of the preceding untreated depressive attack. Admittedly such maintenance therapy has become normal practice even when the symptoms of depression have disappeared. But is it not equally true that there continue to be mood swings after ECT instead of complete remission?

For my part I see no qualitative difference between ECT and Tofrānil in respect of therapeutic activity as it has been described here. The observation of over 200 cases in the Psychiatric Clinic of the University of Lausanne certainly does not indicate any clear-cut difference. Patients previously treated with ECT come out of their depressive attacks under Tofrānil therapy in very much the same way. Generally speaking, the remission is more gradual, but in contrast to our findings with ECT, we have observed no sudden mood reversal immediately followed by a relapse.

In any case, the most useful comparison here can only be with cases of depression recurring more than three times. Dr. Kielholz has shown that the therapeutic response decreases after this, and that mood reversal is then less easily obtained. Indeed among the cases which showed good response to Tofrānil but were no longer cured by or responsive to ECT, we find those patients who have very frequent attacks. These results are best illustrated by profiles such as those shown to us by Dr. Freyhan.

Dr. Kalinowsky has shown clearly that ECT is unable to prevent the recurrence of endogenous depressions, that is, to act upon the process itself. However, he quoted a few instances of attempts in this direction in the form of monthly electroshocks. Similar experiments have been done with Tofrānil which, especially in this direction, seem to us to be of more value. I was particularly struck by this during our clinical tests. So far we have been successful in only three cases, maintained under continuous small doses, in bringing about a change in the periodicity of attacks in patients who have suffered from depression recurring at very short intervals. We are therefore still far from achieving protective effects comparable to those of anti-epileptic drugs.

What seems to be the crucial point in Dr. Kalinowsky's paper on ECT is his marked tendency to limit the number of shocks. He thus makes no attempt to force results by a cumulative effect, except in cases of atypical depression. Nowhere is it so important to keep dosage low or so necessary to watch closely the reaction to the treatment. Professor Steck and I decided to abandon ECT as soon as we started experimenting with Tofrānil, and only once in the ensuing 22 months did we find it necessary to resort to it. We made this decision because we wished to gain experience with a single drug over a fairly long period. It was also inspired, however, by the observation that many depressions occurring before the age of 40 are associated with bioelectric changes and that pathologic changes in the brain are by no means rare at the involutional age. We think this decision will bear fruit since it encourages a more searching diagnosis in place of merely classifying such cases as involutional melancholias. What dictates special caution, however, is the fact that depressed patients are especially sensitive to psycho-organic disorders, no matter how mild. These psychic changes remain while improved techniques have limited to a considerable degree other somatic risks involved in electroplexy.

The neuropsychic complications in Tofrānil therapy should not be ignored. Convulsions, dreaming and mental confusion have been observed. In one case, an epileptic fit led us to make EEG studies which revealed an epileptogenic activity of centro-encephalic type. This patient, a woman, was later to show a typically frontal mood reversal after gas encephalography.

In this connection mention should be made of the role played by encephalo-pneumo-therapy in the French school. This method is indicated particularly in cases of lingering or recurring melancholia. We mention this only for the purpose of stressing the variety of means used to set off a biological reaction at the level of the processes which regulate the vegetative activities. In this respect pneumoshock should

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be more selective than electroshock. Unfortunately the selective effect in practice does not come up to theoretical expectations. The neuropathologist Schaltenbrand has compared electroshock to firing buckshot at the grey nuclei: The impacts are numerous but do not always reach their targets. Other types of biological shock — electro-narcosis, acetylcholine shock and others — have been recognized as having little effect on endogenous depressions. These methods fail to produce psycho-organic perturbations or electric changes comparable to those caused by more intense shock treatments. There are therefore strong reasons for thinking that electroshock cannot be effective without causing organic changes more profound than is generally recognized.

Is any form of psychosurgery effective in depression? Dr. Kalinowsky has referred to investigations in Great Britain which show that depressions of a hypochondriac, chronic and simple endogenous type have been improved by leucotomy. It would be interesting to know which type of surgery has been found most effective.

Developments in the field of brain surgery show that the controversy has not been settled between selective methods and more extensive interventions. In my opinion, these methods should be rejected now that other solutions look so promising.

General discussion from the floor (summarized)

In the general discussion that followed, Dr. Kalinowsky was asked to comment on observations of transient brain changes, first observable after 4-6 ECT's. The EEG usually showed changes at this point and memory changes were often seen. Recently such a change was observed at once after ECT in a patient who had been on Tofrānil. Is it possible that the drug permitted a more rapid appearance of the EEG changes?

It was suggested that since psychotherapy is a high-prestige treatment, no psychiatrist likes to admit that he does not employ it liberally. In fact, however, patients on ECT receive milieu therapy rather than depth or free association psychotherapy.

Another question involved the best procedure to handle anxiety and fear of ECT in patients. The use of curare in this regard was mentioned. The length of the post-ECT amnesic syndrome was also queried. The usefulness of an irreversible treatment such as lobotomy in depression, in view of pharmacological advances, was questioned. The discussant preferred less drastic methods at present.

One discussant commented on depression in old age, and the treatability of many members of this group. North American and British statistics in this regard were compared.

Another discussant asked a theroretical question on the mode of action of convulsive therapy. He wondered what Dr. Kalinowsky thought of the specific denial hypothesis put forward by Weinstein, Kahn and Simm in 1952. Dr. Kalinowsky was further asked at what point he felt ECT should be stopped in regressive ECT.

Another discussant expressed the opinion that although ECT will eliminate any depression it is not indicated in all depressions. ECT may shorten length of illness in a general hospital, but will not work in 50 per cent of the cases where it is given, and when used with success patients remain ill for at least 4 weeks. Tofrānil is often more prompt, and is especially advantageous because it does not produce amnesia. This is an important consideration in patients whose occupation is intellectually demanding. Moreover, there is a link in terms of the continuity of human experience, especially with the doctor, when the patient is on the drug, but this continuity is lost with ECT. The speaker wondered if those who emphasized the safety of ECT would use it on themselves as readily as they would the drug.

Comments on leucotomy were then made. A discussant wondered why this treatment is largely abandoned in America while the results in English patients have been extraordinarily satisfactory. He emphasized that he was not speaking of total cut leucotomy, but of the modified procedure. Between eighty and ninety per cent of the depressed cases have done well on this treatment, especially those with tension depressions and obsessive-compulsive features.

One speaker commented that most patients who rejected shock treatment did so as a rationalized fear of their melancholic illness, which was then projected onto the ECT. Because of this, the manner in which a patient is referred to a hospital is of importance. It is also important that the patient be calm and that he walk rather than be carried to and from treatment. He felt that Tofrānil should be tried first; if it does not work, then ECT should be given, then both together.

Dr. Kalinowsky replied to the questions: He had never favored the theory mentioned in connection with brain changes after ECT. Best ECT results occurred after one or two treatments, and prior to really obvious brain changes. He agreed that EEG changes are often present, but questioned their significance.

In reply to the question about the specific denial theory of ECT effect, he would speculate that the functional psychoses probably involve hypothalamic functioning at some level, and that with ECT something occurs in this area. He is reasonably certain that the ordinary EEG cannot measure the changes that may occur.

In handling the fears of patients in regard to ECT, sedation techniques can be helpful. It is important to distinguish between the patient's feeling of apprehension on waking and his fear of amnesia and disorientation. In reply to the question of when to stop regressive ECT, he favors continuing until urinary incontinence and loss of sense of identity appear. Lastly, he feels that all treatments should be used selectively.

EFFECT OF TOFRĀNIL ON CERTAIN ASPECTS OF THE DEPRESSIVE SYNDROME*

JEAN SAUCIER and CHARLES F. DUMAS**

The depressive states concerned in this communication are limited to those encountered in the out-patient department of the neuropsychiatric service of a general hospital and in the consulting room. In order to simplify an already somewhat complex presentation and for the sake of brevity we have omitted depressions in hospitalized patients and in children. We shall limit ourselves therefore to a brief survey of therapy with Tofrānil† in adult depressive patients not confined to hospital. Our choice of patients has been dictated primarily by the concept of the depressive state, independently of etiology or nosology. We shall not deal with the chemistry, toxicity or pharmacology of Tofrānil since a complete study of this is already to be found in the literature on the subject.

In common with many other investigators, we have noticed the euphoric action of Tofrānil, its variable but on the whole beneficial effects on the neurovegetative symptomatology, the relapses which occur on premature interruption of treatment, and the sometimes spectacular recurrence of the remission on giving the drug again. We have seen the importance of continuing therapy after the remission. Secondary effects — not very common — such as dryness of the mouth and excessive sweating, the variable effect of the drug on psychotic symptoms, on anxiety and on behaviour have also been noted. But most of all we have been struck by the significant modifications we have observed in the sense of time and of the past in our patients. We shall return to this later.

Our clinical material comprised adult persons of both sexes, not hospitalized, with little or no deterioration, with varying degrees of depression and without distinction as regards history of the case, etiology and nosology. The ages ranged from 26 to 79 with an average of 51. Our criteria for the gravity of the condition have not been fixed systematically but they approximate to those given by Lehmann (1) and his co-workers.

About a third of our patients were given, concomitantly or previously, electroshock therapy because of the urgency of the situation as regards the risk of suicide. The majority of these patients received only a limited number of electroshocks. Most of the patients who had already received electroshock therapy on a previous occasion were rapidly improved after 2 or 3 shocks, and improvement was then maintained by Tofrānil alone. Two-thirds of our patients received Tofrānil only. We gave this at first intramuscularly and then by mouth at the beginning of our investigations, but in view of the fact that results by mouth were similar to those obtained intramuscularly we employed only the oral route after April, 1958. The average dose was 150 mg a day, and we never gave more than 250 mg or less than 100 mg a day. The maintenance dose given to all our patients, whether cured, much improved or sufficiently improved to "function" in their habitual environment, was 50-75 mg a day.

In some patients we observed relapse or signs of imminent relapse when we interrupted Tofrānil treatment prematurely. It seems to us too early yet to be able to judge with confidence when the drug can be discontinued without risk of relapse, in spite of our experience with such patients.

The classical criteria for improvement or cure in depressive states are, as we are aware, the change in mood and the return of some degree of optimism, accelera-

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tion in psychomotor responses, raising of the anxiety threshold, disappearance of hallucinations, progressive improvement in interpersonal relationship, improvement in sleep and appetite and increase in weight. All these criteria are sufficiently objective not to escape the attention of even the least experienced observer.

Before considering other means of evaluating cures it is worth noting that endogenous depressions, the manic-depressive type, and involutional melancholia, respond favourably to Tofrānil in more than a third of the cases, but neurotic depressions respond poorly. Mixed psychoneuroses with hysterical, obsessional and hypochondriacal elements were completely unaffected in our series of cases, and the same applied to depressions associated with schizophrenia, depressions of old age, and those associated with paranoid states and organic cerebral lesions.

Our results are shown in the accompanying table. These figures agree well with those obtained by other authors except that the improvements in endogenous depression and failures in depressions associated with mixed psychoneuroses seem even more sharply contrasted in our statistics. Between these two extremes lies an intermediate group of neurotic depressions or depressions associated with other morbid conditions. We were considerably struck by this grouping.

Diagnosis	Number of Patients				
	Cured	Much improved	Improved	Not improved	Totals
Manic-depressive psychosis	14	8	5	2	29
Involutional melancholia	1	1	2	1	5
Reactive neurosis depressions	1	2	8	7	18
Mixed psychoneuroses				10	10
Schizophrenic reactions		1		3	4
Depressions in old age				2	2
Depressions associated with paranoid disorders			1	3	4
Depressions associated with organic cerebral disorders			1	3	4
Totals	16	12	17	31	76

We have to admit that our statistical data based on empirical clinical findings lack the strict accuracy of quantitative measurements and the dogmatic appeal of a double blind test. Nevertheless they were obtained by two observers with differing personalities, working separately on two different groups of patients, the sole criterion for the administration of Tofrānil being the existence of a depressive syndrome. The results observed in each group — 45 and 31 cases respectively — are identical. In our view it is more logical to explain this identity as a statement of fact than as a similarity of errors and interpretation.

What is the explanation of these statistical results? At first we had expected a uniform improvement in depressive states treated with Tofrānil. We hoped that the common denominator among all our patients, the depression, would diminish in similar ratio among all groups. To our surprise this ratio was not revealed in relation to the depression as such but was revealed in relation to different diagnostic data. Thus the depressive syndrome of despondency, tears, asthenia, adynamia, loss of interest, etc., common to all our cases remained unchanged in the organic diseases, in the paranoid reactions, mixed psychoneuroses and schizophrenia, improved noticeably in the neurotic depressions and almost always improved in the depressive states of manic-depressive psychosis.

These facts have caused us to question the psychiatric concept of depression and the presumed mode of action of Tofrānil. Consequently the definition of depression requires some revision. We already know that the concept must not be confused with that given by physiologists. There are far too many definitions of depression. Some are too simple, some too elaborate. We have taken the simplest from Régis (2): "Depression is a reaction of sadness, active or passive, with diminution of spontaneous action, sometimes to the extent of complete suspension of all activity and sometimes accompanied by agitation."

Ey (3) has formulated a more complete definition in connection with melancholia: "A depressive state, generally paroxysmal, characterized by a despondent toning of the contents of consciousness, lack of will, intellectual inhibition, pessimistic ideation and anxiety."

Sullivan (4) is more laconic: "Depression is a preoccupation of consciousness, nourished by ideas of gloom and involving considerable reduction of activity."

Diethelm (5) sums up the essence of depression thus: "A pathological disturbance of mood, related to Kraepelin's manic-depressive psychosis, involving genetic and psychodynamic elements."

For Binswanger (6) the essential elements of the psychopathology of depressive states of endogenous origin are their ultimate determination by the past and "the supremacy of what has been."

In current language the term depression qualifies a state common to different morbid conditions, in which the intensity varies from that of a simple depression to a state of stupor.

In view of the results obtained, and from the hypothesis that Tofrānil acts directly on the element of depression, we have to realize the disparity between different forms of depression, since we cannot otherwise account for the selective antidepressive effect of Tofrānil. It is possible, on the other hand, that the unity of depressive syndromes put forward here is only an apparent one, for we can visualize that Tofrānil is not just a depressive or antidepressive agent but perhaps modifies certain depressogenic factors.

Analysis of our cases enables us to find a common clinical denominator applicable to all those that improved. In fact, apart from the feeling of guilt-ridden grief, the episodic agitation, pessimistic mental content, etc., we were struck by the frequent allusions of our patients to their experience of time and to their feeling about the absence of passage of time. They gave the impression of living in a state of arrest, of mentally marking time in a situation where the only existential modality seemed to be a continual reliving of the past. They appeared to be unable to inject themselves into the reality of the present and incapable of integrating themselves into the perspective of the future. The first step toward progress, noticed by those around them before they remarked it themselves, was the entrance of these patients into the reality of the present. Next, their progress toward normality was emphasized by their ability to reshape the past, which already appeared less formidable against a background of future possibilities.

This constant presence of the element of time seems to us to transcend the depressive phenomenon, and throws doubt on the opinion commonly held that mood is the primary factor in depression. In our experience the depressive phenomena seem to be secondary to a more fundamental alteration of the personality where the basic disorder is one of consciousness of subjective time. By modifying the disturbed state of consciousness, Tofrānil may cause a disappearance of depressive symptoms which are merely secondary to the disorder of temporality.

This psychopathological hypothesis would be in line with the existential concept of mental disease.

Finally, on a physical basis, the diffuse perception or feeling of subjective temporality might be localized hypothetically and through semeiological analogy in the neighborhood of the arousal center, i.e. in the pedunculo-hypothalamic region. In this case, if we pursue the same hypothesis, the present would become more re-enacted, as it were, whereas the past would become dormant and blurred.

This broad hypothesis, in spite of its gaps, seems promising enough to tempt us to pursue our observations in a definitely biopsychological direction.

Résumé

Les auteurs rapportent les résultats de l'observation de 76 cas d'états dépressifs traités par le Tofrānil. Dans l'ensemble, ces résultats sont sensiblement comparables à ceux qui furent publiés jusqu'à maintenant; cependant, les auteurs ont été frappés par l'action sélective du Tofrānil sur certains états dépressifs — les dépressions endogènes en particulier — et par l'échec relatif de son action dans les dépressions névrotiques, simples et associées à d'autres modalités névrotiques, de même que dans les dépressions schizo-affectives, séniles, paranoïdes ou associées à d'autres maladies organiques. Ils croient voir une corrélation entre les succès du Tofrānil et la pathologie du *temps*. Ils suggèrent l'hypothèse que le désordre de la conscience temporelle subjective pourrait être à l'origine des dépressions endogènes et que le Tofrānil modifierait primitivement ce désordre initiateur des états dépressifs.

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PRELIMINARY EVALUATION OF TOFRĀNIL IN A COMBINED IN-PATIENT AND OUT-PATIENT SETTING

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Introduction

Tofrānil† is one of several drugs being investigated simultaneously by the same team on the research ward of a psychiatric hospital and in the out-patient clinic of a large metropolitan general hospital. A section of the psychiatry department of the clinic has been set aside exclusively for the evaluation of new psychopharmacologic agents.

There are several advantages in using these two sources of patient material. A broader spectrum of mental illness is available for study. In addition, continuous follow-up is more easily arranged since patients can be freely interchanged between both facilities. In the event that an out-patient decompensates and develops an acute psychotic episode, he can be hospitalized immediately. In addition, hospitalized patients can be followed in the drug clinic after discharge without interruption of their treatment. Since the same staff is used for evaluation and treatment in both installations, administrative snarls are minimized and the variables associated with changing raters are lessened.

In this brief presentation we are reporting on our preliminary experience with Tofrānil as an anti-depressant agent. Our studies are in the pilot stage and no controls or follow-ups have as yet been done. Several of the patients are still under treatment and their conditions will be reported as they were at the time this paper was written.

Material and Method

Thirty-nine patients were studied. Of this number, 19 were in-patients and 20 were out-patients. Age range and sex distribution were similar in both groups (Table 1). Females outnumbered males in a ratio of 2:1. In-patients had a somewhat longer history of illness than out-patients but the majority of both groups had been ill for many years.

TABLE 1
Characteristics of patients receiving Tofrānil

	In-patients	Out-patients
Age range	28-66 yrs.	17-60 yrs.
Sex	F.-13 M.-6	F.-13 M.-7
Duration of illness	1 mo. to 30 yrs.	1 mo. to 10 yrs.
Average duration of illness	7.4 yrs.	5 yrs.

Target symptoms rather than diagnostic categories were used in selecting patients. With the exception of the first five out-patients chosen for treatment, the presence of depressive symptoms was the sole criterion for the choice of patients. These initial 5 patients had been selected to determine the effect of Tofrānil on target symptoms *other* than depression and were *not* depressed. They were included

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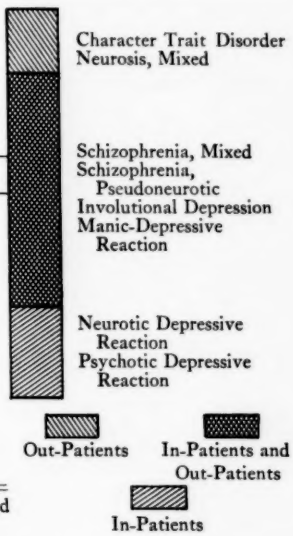
separately for the sake of completeness (Table 2). The diagnostic categories form an overlapping spectrum. Certain categories such as the character disorders and the mixed neuroses are seldom seen in a mental hospital but are more common in a general hospital out-patient clinic. On the other hand, psychotic and neurotic depressive reactions are rarely seen in the out-patient clinic for any length of time since they

TABLE 2
Diagnoses and distribution of patients receiving Tofrānil

In-patients	No. of patients
Psychotic depressive reaction	6
Schizophrenia, mixed	5
Neurotic depressive reaction	3
Involutional depression	3
Schizophrenia, pseudoneurotic	2
Total	19
Out-patients	
Schizophrenia, pseudoneurotic	5
Character trait disorder	3
Schizophrenia, mixed	2
Involutional depression	2
Neurosis, mixed	2
Manic-depressive psychosis	1
Total	15
Schizophrenia, mixed	2
Neurosis, mixed	2
Schizophrenia, catatonic	1
Total	5*



*These five patients were *not* depressed and were being evaluated for other target symptoms.

are usually quickly hospitalized as soon as their depressions become severe. There are both social and medical factors to explain these findings which we cannot explore further in this paper. We also observe a large overlap of diagnostic categories that are found about equally in both mental hospitals and out-patient clinics.

Dosage level and methods of administration differed slightly between in-patients and out-patients (Table 3). In-patients received higher dosages of the drug since we could observe them more carefully. In-patients were started on placebo, one tablet

TABLE 3
Oral dosage data on patients receiving Tofrānil

	In-patients	Out-patients
Daily dosage range	75-375 mg	75-200 mg
Mean daily dosage range	167 mg	105 mg
Range of time on drug	23-140 days	14-110 days

three times a day for a week and then begun on the active substance during the second week. They received 25 mg three times a day during this second week, a dose doubled during the third week to a total of 150 mg daily. Thereafter the dosage was elevated or reduced in accordance with the clinical response and the severity of any side effects which might have developed. Three in-patients received the drug intramuscularly in doses of 25 mg three times a day. Out-patients were given the

TABLE 4

Improvement ratings on Tofrānil by diagnosis

	In-patients				*Out-patients*			
	Much improved	Moderately improved	Slightly improved	No improvement	Much improved	Moderately improved	Slightly improved	No improvement
Psychotic depressive reaction	—	—	2	3	—	—	—	—
Neurotic depressive reaction	1	2	—	—	—	—	—	—
Schizophrenia, mixed	—	4	—	1	1	—	—	1
Schizophrenia, pseudoneurotic	1	1	—	—	2	—	—	3
Involutional depression	—	1	—	2	—	1	—	1
Manic-depressive psychosis	—	—	—	—	—	—	1	—
Character trait disorder	—	—	—	—	1	2	—	—
Neurosis, mixed	—	—	—	—	—	—	—	2
	2	8	2	6	4	3	1	7
	Total—18*				Total—15			
Schizophrenia, mixed					—	—	—	2
Neurosis, mixed					—	—	—	2
Schizophrenia, catatonic					—	—	1	—
					0	0	1	4
					Total—5**			

*An additional patient could not be rated (see text).

**These cases were not depressed and were being evaluated for the effect of Tofrānil on other target symptoms.

drug only by mouth. Out-patients were also started on placebo for a week when their clinical condition permitted. Starting with the second week they received active substance, 25 mg three times a day. They were then gradually raised by 25-mg increments to a dosage level where optimal clinical effects were observed or until troublesome side effects developed.

In-patients were interviewed daily on rounds. In addition their clinical progress was discussed three times a week in a special drug conference composed of psychiatric, medical and nursing personnel. Side effects were investigated in collaboration with an internist. Vital signs were recorded daily. Out-patients were evaluated weekly in the drug clinic through a clinical interview in which the patient's total life adaptation as well as fluctuations of the initial target symptoms from the base-line were considered in arriving at an improvement rating. Both in-patients and out-patients received a baseline C.B.C., complete urinalysis and alkaline phosphatase determination which were repeated at weekly intervals throughout the course of the study.

Results

(*a*) *Clinical Response* — Thirteen of the 19 in-patients experienced varying degrees of relief from their depressive symptoms after receiving Tofrānil (Table 4). One of these patients had experienced a slight improvement after a course of electroshock therapy prior to being started on the drug. Even though his improvement became more marked after receiving Tofrānil, he was not included among the improvement ratings because of the difficulty in determining what part each type of treatment contributed to his improvement. Eight of the 15 out-patients with depression as a target symptom improved. There appears to be no clear correlation between improvement in depressive symptomatology and diagnostic category after therapy with Tofrānil.

The improvement described in all cases was manifested by an elevation of mood, a diminution in psychomotor retardation and greater ability to concentrate. Affect became more spontaneous and appropriate. Ideational content did not undergo any marked qualitative alteration. The most significant changes noted in ideation were a diminution in self-derogatory thoughts and obsessive-ruminative trends. It was not uncommon for both therapists and nurses to comment that as some of these in-patients improved, they became more outgoing and responsive to ward activities and psychotherapeutic suggestion and support. The patients described their mood as elevated and their outlook for the future as more hopeful.

We do not feel, however, that these changes are specific for Tofrānil since we have seen similar improvements with other forms of treatment, including electric shock. In our series, however, several of the patients had received other medications and electroshock therapy previously without benefit. There were several other patients, however, who did not improve with Tofrānil but did respond to a later course of electroshock. Two patients with somatic manifestations of depression and one patient with depression secondary to severe obsessional rumination have shown unexpected improvement after failing to respond to 3 or 4 medications. It should also be kept in mind that even though the total number of patients improving in both in-patients and out-patients is not spectacular, those who did improve had usually been ill for a number of years and had received many types of treatment without appreciable gain. Such facts are too often obscured in a purely statistical evaluation of treatment results.

Three in-patients were started on intramuscular medication for 7 to 18 days prior to being switched to the oral form. Two showed a rapid and significant improvement. One did not. Therefore, our results with intramuscular Tofrānil are still inconclusive.

In patients responding to Tofrānil, both subjective and objective improvement was manifested within 3 to 5 days after starting the medication and usually reached an optimal peak within 2 weeks. Appetite improved and weight gain from 2 to 10 lb. was noted in a number of patients. Sleep patterns showed slight improvement in that patients were less likely to experience early morning awakening but sedation was still required in most of our in-patients although in reduced quantities.

Depression characterized by the target symptoms of sadness and melancholy, pessimistic rumination, feelings of worthlessness, psychomotor retardation, and vegetative disturbances resulting in anorexia, weight loss, constipation and insomnia has thus far shown the best response to Tofrānil in both patient groups. But results are not always consistent and further research is necessary to determine the constellations of target symptoms most affected by this drug and the optimal dosage levels at which improvement develops.

TABLE 5
Side effects with Tofrānil

Side effect	In-patients	Out-patients
Hepatitis	0	1
Acute myocardial infarction	1	0
Urinary retention	1	0
Increased anxiety	3	6
Nausea	1	3
Dry mouth	2	4
Vomiting	1	2
Epigastric distress	0	2
Constipation	0	2
Diarrhea	1	0
Postural hypotension	0	1
Dizziness	1	1
Increased diaphoresis	1	1
Edema of face and eyes	0	1
Ankle edema	1	0
Blurred vision	1	1
Palpitation	0	1
Akathisia	0	1
Erythematous rash	0	1
Ringing in ears	1	0
Loss of equilibrium	1	0
Lethargy	1	0

(*b*) *Side Effects* — Side effects were common although few were serious (Table 5). Complications which are potentially serious have been italicized. Side effects were much more common among out-patients than in-patients. Only 8 of the 19 in-patients reported side effects while 15 out of 20 out-patients reported them. In-patients most commonly developed side effects between 100 and 375 mg daily. Most of the out-patients developed side effects on 75 mg daily. Lehmann, Cahn and de Verteuil have expressed the opinion that side effects can be eliminated by keeping the dosage level of Tofrānil under 200 mg daily(1). Since none of our out-patients received a dosage level higher than 200 mg daily, our findings do not bear out their impression.

One in-patient had to be taken off the drug after 12 days because of acute urinary retention on a dose of 100 mg daily. Urinary flow returned to normal within 36 hours after the drug was discontinued. 3 out-patients had to be discontinued after 7 days because of increased anxiety and agitation. One of these patients developed an akathisia reaction very similar to those seen in association with the administration of certain phenothiazines, during which she could not sit or stand still.

It has been our experience that while some patients showed a mood elevation with Tofrānil accompanied by a lessened concern over previously dominating obsessional and phobic material (the so-called "chemical lobotomy effect"), other patients did not experience any sustained or accompanying tranquilizing effect. In the latter group, environmental stress could precipitate a bout of anxiety and hyperactivity, which usually subsided when the stress was removed. In two instances there was an excessive shift from a depressed state with motor retardation to a hypomanic state with no period of normalization in between. We have also seen this occur with iproniazid.

Jaundice in conjunction with Tofrānil has previously been reported by Kuhn(2) and Lehmann(1). While we cannot be absolutely certain that the hepatitis in our out-patient was connected with the drug, the lack of involvement of other medication, the absence of injections for several months prior to the episode, the mildness of the course of the disease and the rapid clearing within 10 days after the drug was discontinued are strongly indicative of a drug-induced hepatitis. The patient was a 45-year-old male with a previous history of heavy alcohol intake although he had stopped drinking six months before the hepatitis developed. Liver function tests performed at that time during a routine physical examination were negative, although the patient's liver was slightly enlarged. He had been on a dose of 200 mg of Tofrānil daily for 110 days when the hepatitis developed. It is possible that patients with a previous history of liver or gall bladder disease or heavy alcohol intake might be more prone to the development of hepatitis with Tofrānil. It is our experience that patients with a similar history of liver or gall bladder involvement being treated with phenothiazines are more prone to the development of jaundice than patients without such history.

It will be noted in Table 5 that one of our in-patients developed an acute antero-lateral myocardial infarction while being treated for depression with Tofrānil. The patient was a 55-year-old widow with an 8-year history of hypertension recently ranging between 210/110 and 290/130. A routine EKG prior to ECT 2 months before Tofrānil treatment was negative but mild cardiac enlargement was noted on X-ray at that time. The infarction developed after the patient had been receiving 75 mg of Tofrānil daily for 7 days. Just as Lehmann reports that the one cardiac death in his series cannot be directly attributed to Tofrānil, we cannot say there was a causal link between the drug and our patient's cardiac episode. Nevertheless, we feel these two experiences dictate caution in the administration of Tofrānil to patients with a history of marked hypertension or cardiovascular disease.

Laboratory findings remained within normal limits except for 4 patients who developed alterations in their alkaline phosphatase responses. Three in-patients went from "normal-borderline" to "borderline" and the out-patient with jaundice went from "normal" to "pathological." All returned to normal on discontinuing the drug.

Conclusions

Our preliminary experience with Tofrānil in a pilot group of 39 psychiatric patients leads us to be cautiously optimistic about its future as an antidepressant. But further research is necessary in several important areas before a final evaluation can be reached. These areas include:

1) The constellation of target symptoms most responsive to the drug.
2) The dosage range for both in-patients and out-patients over which optimal anti-depressant effects are observed.
3) The development of tolerance to the drug.

4) The incidence, severity and time of onset of side effects, especially in relation to the hepatic and cardiovascular systems.
5) The relative effectiveness of Tofrānil when compared directly in controlled studies with other forms of anti-depressant therapy.

Résumé

Le Tofrānil est un des médicaments essayés simultanément sur les malades mentaux d'un hôpital, et sur des patients en traitement ambulatoire, par la même équipe de psychiatres, en vue de déterminer sur une large échelle de cas son efficacité en tant que moyen antidépressif.

Trente-neuf sujets ont été étudiés, soit 19 cas hospitalisés et 20 ambulatoires. Mis à part 5 de ces derniers, le choix a été basé sur l'existence d'une dépression comme symptôme prédominant, sans égard au diagnostic. Les critères d'évaluation et de sélection des patients sont décrits en détail dans le texte. Treize hommes et 26 femmes, entre 17 et 66 ans, ont reçu de 75 à 375 mg de Tofrānil par jour, durant des périodes allant de 1 à 20 semaines. Des manifestations secondaires sont apparues chez 8 cas d'hôpital sur 19, et 15 cas ambulatoires sur 20. L'épreuve a dû être interrompue au bout d'une semaine chez 3 cas ambulatoires, par suite d'une augmentation de l'anxiété et de l'agitation motrice. Il en a été de même au bout de 12 jours chez un malade hospitalisé, une rétention urinaire s'étant déclarée. Une acathisie est apparue chez un patient ambulatoire. Six fois l'état anxieux s'est aggravé, 4 sujets ont présenté des nausées, 3 autres des vomissements, 2 se sont plaints de malaises, siège épigastrique, de sudations pathologiques et de constipation. Les autres effets secondaires notés sont l'hypotension de posture, une éruption érythémateuse touchant le visage et les épaules, de l'oedème de la face et des paupières, une vision floue, des bourdonnements d'oreilles, et de l'oedème malléolaire. Chez quatre patients la phosphatase alcaline a passé d'une "valeur à la limite de la normale" à une "valeur extrême": chaque fois l'interruption de la médication l'a ramenée à sa valeur normale. La plupart des manifestations secondaires sont apparues pour des doses de moins de 200 mg par jour.

D'une manière générale, les patients du dehors recevaient des doses plus faibles que les malades hospitalisés, mais les effets secondaires se sont manifestés chez eux avec une fréquence presque égale. Pour apprécier l'amélioration, les auteurs se sont basés sur l'apaisement de la dépression et l'adoption de réactions mieux adaptées. Sur 19 cas d'hôpital, il y a eu 2 bonnes améliorations, 8 améliorations modérées, 2 améliorations légères et 6 insuccès. Quinze cas ambulatoires présentant des signes de dépression ont donné 4 succès marqués, 3 modérés, 1 amélioration faible et 7 échecs. Plusieurs de ces patients avaient été traités auparavant déjà, et sans résultat, par d'autres médicaments ou par la thérapie électroconvulsive. Deux malades présentant des manifestations somatiques, et un autre dont la dépression était secondaire à une grave obsession, ont été améliorés contre toute attente. Un certain nombre de sujets améliorés étaient malades depuis plusieurs années.

Bien que notre expérience du Tofrānil soit limitée, et que l'étude d'un nombre de cas beaucoup plus élevé soit nécessaire avant qu'il soit possible d'en apprécier exactement la valeur, les auteurs se montrent optimistes, quant à son avenir en tant qu'agent antidépressif.

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General discussion from the floor (summarized)

Dr. Malitz, in replying to a question whether complications occur more in patients who do not improve, said he felt that this was true, and that it was because the dosage level tends to be raised in such patients and hence more frequent side effects are seen. Further, he felt that certain anxiety effects may be triggered by the drug but are not directly due to drug effects, especially in out-patients who are not closely supervised. For example, certain patients may develop hyperhidrosis, dry mouth, or flushing; this may be very anxiety-provoking and may lead to the development of tachycardia and hyperactivity. He further stated that out-patients tend to tolerate the drug less well than in-patients, and that this may be due to the fact that they are under greater stress and react more to it. This raises an important question in connection with the ability of the therapist to convince the patient to carry on with the drug.

THE USE OF TOFRĀNIL IN THE AGED

D. Ewen Cameron*

In approaching this problem, it is necessary to state certain general premises, most of which are supported by a reasonable but not yet complete amount of experimental work.

The first is that stress tolerance decreases with age. This is true of stress of all kinds, whether environmental, intrapsychic or physiological. It is also true of a considerable range of living organisms quite apart from man. Grad and Kral (1) have shown that the capacity of the aged organism, in this instance the mouse, to withstand exposure to cold is very considerably less than that of the young animal. Temperatures can be selected which will result in the death of an entire group of aged mice, whereas the younger mice will have a survival rate up to 50%. For this reason — that is, that stress tolerance decreases with age — it is commonly stated that the reserves of the older person are less adequate; and clinical procedure has long established the necessity of limiting the severity of diagnostic and therapeutic procedures to be carried out in the aged person. It is recognized, too, that the aged individual must have more extensive rest: in a word, he must be protected as far as possible against stress.

The second premise is that with passing years an increasing number of defects appear in the functioning of the older individual. These defects may take the form of memory failure, of aphasias, of cardiovascular decompensations, of failures in kidney function. These failures frequently become partly or completely compensated, the individual endeavouring to maintain a good level of performance by a variety of means, such as avoidance of stressful situations, frequent resting, the use of mnemonics and of less demanding ways of carrying out motor activities. In these circumstances, many of the defects may become latent, and it is only under stress that such a latent defect in the older person may become overt. Indeed, the older individual frequently evinces great anxiety if circumstances seem likely to lead to his defects becoming apparent, this forming the basis of Kurt Goldstein's concept of the catastrophic reaction (2).

The third premise is that if, nonetheless, stress is applied to such aging individuals in whom reserve capacities are limited and who are carrying a rising number of defects, then, when stress reaches a critical point, disorganization (3) occurs. By disorganization is meant a breakdown in the pattern of behaviour developed by the patient whereby the defect and the limited reserve can be compensated. Once disorganization has occurred, the latent defects will now become overt, and the patient may show clearcut memory failures, failures in his conceptual abilities, visual and auditory inadequacies, provided there were underlying compensated latent defects. The most common disorganizing factor in the aging individual is mood swing, and the most common deviation of mood is in the direction of depression.

This brings us to our fourth and last premise: namely, that in the aging individual there is a progressive decline in the capacity to experience pleasure. This is seen in the decline in the ability to get satisfaction from eating, from sexual relations, from listening to music, from physical activities — all of which in the past may have afforded him quite intense pleasure. The nature of this decline is not yet fully understood but it would seem, certainly in part, to be dependent upon changes at the point of sensory input. For instance, the taste buds in the aging person are said to be much fewer than they were when he was in his middle years (4).

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Consequent upon this decline in pleasure, there is naturally a decline in the incentive to undertake both well-established activities and new things, so that the individual's range of doing and experiencing becomes more and more circumscribed. Until recently, it has been commonly believed that the decline in enterprise in the older person was largely due to his growing sense of insecurity. However, one may point to at least three major factors contributing to his narrowing range of activity. The first is the one to which reference has already been made: namely, the decline in pleasure, that is, in reward for doing things. The second is his growing sense of insecurity. And the third is our cultural anticipation concerning the role of the aged individual. As is well known, until very recently the dominant concept of the aging individual in our society has been one of a progressive decline in the individual's powers and his gradual retreat into the chimney-corner. The influence exerted by widely held concepts in any society, especially where they have been incorporated by the individual into his own value system, is quite outstanding and hence still further augments the growing inactivity of the individual. This finally results in the setting up of an in-spiralling feedback system whereby a declining motivation to do things results in the individual doing less, and his doing less results in an increasing disuse atrophy of his power to do things.

All of this creates in the aging individual a growing sense of frustration, and from this comes, not unnaturally, a feeling of depression and unhappiness and displeasure.

This report is concerned with the use of Tofrānil* in 6 aging patients, in 5 of whom positive and favourable effects were obtained. The following is a brief notation about each case:

Case 1: This woman, then aged 59, was admitted to the Allan Memorial Institute for the first time on February 14, 1956 and was discharged on March 16th, 1956. She complained at that time of feelings of depression which came on subsequent to an attack of influenza in September, 1955. She had crying spells, slept poorly and began to drink excessively in order to keep herself going. She made an abortive suicidal attempt. Studies carried out at the Institute revealed that among her neurotic elements there were marked feelings of inadequacy and repressed hostility particularly with respect to her husband. She did well, primarily on psychotherapy, and was discharged with a diagnosis of character neurosis with periodic neurotic depressions. In May 1957 she had a mild stroke with resultant slight interference with speech and slight weakness in the right side of the body. This was repeated two or three months later. She was readmitted to the Institute on October 4, 1957 and discharged on November 1, 1957. She had mild, right-sided neurological signs and showed a moderate arteriosclerosis. A diagnosis was made of (1) long-term character neurosis with periodic depressions, (2) an emerging organic brain syndrome, and (3) a vascular or atrophic lesion involving the left frontal area. Abnormal activity arising in the left mid-temporal area was noted in the electro-encephalogram.

The patient now began gradually to decline in her activities. She complained that she could not use her right arm and gave up knitting. She complained of her inability to concentrate; she would not undertake even light gardening, and she began to show an increasing incontinence, together with recent-memory deficits. An air encephalogram was carried out in August, 1958, and an area of atrophy in the left frontal area was found. At the end of August, 1958, it was decided that insofar that she seemed to be extremely underactive and seemed to be giving up more than her neurological symptoms warranted, she should be put on Tofrānil, 25 mg q.i.d. Within three weeks it was reported that she was much better, her speech was clearer, she now wanted to do things, she was walking better and did

*Trade Mark.

not get so tired as before. Her interest in things had begun to return and she was now beginning to work more in the garden and in the house and was also sleeping better. In addition, her husband thought that she was able to remember things more adequately than before. She returned to forward planning and began to mix better with her friends. The Tofrānil was increased to 50-25-50-25 mg and has been maintained at that level since then. The increased activity and interest have been sustained.

The important thing which this case demonstrates is that this patient, who clearly has a slowly progressive organic condition, is able, nonetheless, to make better use of her assets once the mild, pervasive depression has been brought under control by Tofrānil.

Case 2: This 65-year-old widow was admitted to the Allan Memorial Institute for the first time on January 30, 1957, remaining until March 29, 1957. Her primary complaints were anxiety and depression. She was treated with electroshock, sex hormones and somnolent insulin, and made a tolerably good recovery, but relapsed soon thereafter. She was readmitted on April 17, 1957, remaining until August 24, 1957, and at that time was diagnosed as suffering from a depression occurring in a long-term psychoneurotic individual. She improved only to a limited extent in hospital. Following upon this she was put on an ambulant basis, and a long series of agents was used in an attempt to control her loss of pleasure in life. She was put on somnolent insulin and nitrous oxide, hormones were used, psychotherapy was employed, and vitamins C and B_{12} were used in massive amounts.

By December, 1957, she was perhaps less irritable and sleepless but still felt unhappy. She was started on iproniazid 50 mg t.i.d. on December 27. This was continued until February 12, 1958 without any definite improvement. She found it difficult to keep any nursing companion-housekeepers with her, she dressed sombrely, had very few social contacts, and had a great variety of somatic complaints.

On April 8, 1958 she was started on Tofrānil, 25 mg q.i.d. On May 8, 1958 we noted that she smiled more frequently, although she was still quite complaintive. By May 30 she had had an 8 lb. weight gain since she had been put on Tofrānil; she was very much better than she had been, less depressed and, in fact, showed practically no depression at all. She slept well and said her appetite was very good.

By June 25, 1958 she was feeling considerably better, more lively and energetic; she was continuing to gain weight; she still had some slight degree of morning depression. On September 30, 1958, we increased the Tofrānil to 75-50-75-50 mg. She seemed to grow rather more tense and to sweat a good deal and hence, on October 28, the dose was cut back to 50 mg q.i.d. Chlorpromazine was given in amounts of 50 mg in the morning and 25 mg t.i.d., starting at mid-day, and in this way we succeeded in cutting down the sweating considerably. In December, 1958 we found that she had gained 17 lb. in the year.

Despite the fact that aging symptoms are slowly progressing, such as memory deficits, she is certainly maintaining herself at a much higher level than she did prior to the administration of Tofrānil. Special emphasis should be laid upon the extent to which Tofrānil is of value both in cutting down the depression and in increasing the range of this woman's activities as well as increasing her general friendliness.

Case 3: This 74-year-old woman suffered for 15 years from rheumatoid arthritis and has had a variety of forms of cortisone. About a year and a half ago she began to show rapidly increasing emotional instability and impoverishment of recent memory. She was almost completely bedridden, and she had great periodic outbursts of antagonism. A variety of sedatives and tranquilizers were used in an attempt to cut down the emotional swings but these failed. As these swins beg-

came more severe, the patient became confused and actually delusional during them, making accusations of infidelity against her 76-year-old husband, being quite disoriented with regard to her location. She was put on Tofrānil, 25 mg q.i.d., in January, 1958 with, at first, considerable improvement, the patient now showing fewer emotional swings, becoming increasingly well oriented, and having more energy so that she was able to get up and go out on one or two occasions. However, the organic process was quite rapidly progressive; there ensued repeated minor cerebral accidents, apparently involving the left side of the brain, with subsequent difficulty in speaking and inability to use her right hand. Despite continuance of Tofrānil, the emotional swings became more marked, and her confusion and paranoid distortions more severe, to the point where her commitment was necessary.

From this case can be seen the definite limitation (which of course is to be expected) in the capacity of Tofrānil to control an organic state which is progressing rapidly.

Case 4: This 66-year-old woman has been admitted to the Allan Memorial Institute on four occasions, the first time being on June 22, 1955. About the summer of 1955 she had begun to forget the names of people and dates and had become quite depressed about this. She was diagnosed as suffering from an organic brain syndrome, senile psychosis. As far back as 1954 occasional paranoid trends would appear and the patient would become excited but never seriously unmanageable. But in September, 1958 the patient's condition progressed to the point where she would have states of excitement, lasting several days, in which she would accuse those around her of stealing things from her and become quite threatening.

In consequence of this, the patient was put on Tofrānil, 25 mg q.i.d., on February 22, 1959. Subsequent to this her irritability, and consequent confusion and paranoid thinking greatly subsided. It became possible to carry her on an ambulant basis whereas prior to the administration of Tofrānil it had appeared almost certain that she would have to be committed. Her memory defects showed little tendency to clear up. It is perhaps to be noted that in her case a major factor in her memory defect is a serious tendency to perseverate, which appears within about two minutes after testing has been initiated.

The important thing to note here is that where the organic process is not too severe, the emotional swings apparently can be stopped. How this is achieved is unclear, unless it could be that the emotional swings (or the emotional lability, as it is more technically termed) depend primarily on an inability to stop a swing once started, and Tofrānil may prevent the actual onset of the swing. It is doubtful, as seen in Case 3, that it can actually block or buffer a swing once it is established.

Case 5: This 72-year-old married woman was admitted to the Allan Memorial Institute for the first time on September 23, 1958. Her primary complaint was of depression (which was worse in the morning) of about a year's duration. She felt increasingly tense and anxious, and complained of a nervous stomach. There was insomnia of the early-waking variety and decrease in appetite; there was also frank rumination concerning suicide. There was not any serious memory deficit.

She was started on Tofrānil, 25 mg q.i.d., on September 27, 1958. Because of the complexity of her depression, electroshock therapy was commenced on October 6, 1958. It is noteworthy that the patient began to improve after her first treatment, which is quite unusual in these more difficult and involved senile states. Tofrānil and electroshock therapy were interrupted by the appearance of fever and the patient was found to have a pneumonic process. Treatment was re-established and was brought to a satisfactory conclusion by November 23, 1958.

The point of importance here is that the combination of electroshock and Tofrānil seems to have exerted a favourable influence.

Case 6: This 82-year-old single man was admitted to the Allan Memorial Institute on September 27, 1958 for the first time. He had come as a transfer from the Department of Surgery, to which he had been admitted on December 23, 1957, having been knocked down and injured by a car. He had suffered a comminuted fracture of the left tibia and a compound fracture of the left humerus as well as lacerations of the arm and chin. Throughout his stay in that department the patient had been extremely difficult with regard to nursing management: he got out of bed before his left leg was fully healed and collapsed on the floor, with resulting damage. He was stubborn to a degree and presently began to defecate in his bed. Because of his unmanageability he was transferred to the Allan Memorial Institute.

There was little evidence that his memory had been impoverished before he came to us but much evidence that he had shown lifelong traits of obstinacy and aggressiveness. He remained in his room, would not get out of bed, and showed a very considerable decline of interest and activity but no frank depression. Because of this, he was started on Tofrānil, 25 mg q.i.d., on October 7, 1958, but by October 27 — at which time he was getting Tofrānil, 75 mg q.i.d. — he developed visual hallucinations. Tofrānil and Somnol, which contains some hyoscine, were discontinued. His hallucinations ceased shortly thereafter.

During the time that Tofrānil was in operation, this patient did show considerably more activity, was more accessible, would get out of bed and seemed more friendly. The Tofrānil was not reinstituted after the hallucinations disappeared, but we were able to continue and to expand the gains already made, to the point where he could be discharged home, considerably improved.

Conclusion

In conclusion, we may say that these various cases suggest that Tofrānil may be of value in the aged insofar as it alleviates a rather unspecific type of mood disturbance where it exists, the chief characteristics of which are depression, withdrawal, irritability and affective swings. With regard to the latter, its powers are quite limited; and with respect to a rapidly progressive organic syndrome it has naturally no influence whatsoever. But where it alleviates the type of mood disturbance described above, one frequently finds a valuable return in activity, interest, memory and judgment.

Résumé

En abordant ce problème, il est nécessaire de poser certains principes généraux, dont la plupart sont étayés par une documentation expérimentale importante, bien qu'encore incomplète.

Le premier principe est que la tolérance de l'organisme aux chocs diminue avec l'âge. Ceci est vrai pour toutes les formes de chocs, qu'ils soient extérieurs, intrapsychiques ou physiologiques. C'est pour cette raison que l'on parle d'une moins bonne adaptation des forces de réserve des vieilles gens. De même, l'expérience clinique a depuis longtemps mis l'accent sur la nécessité qu'il y a d'éviter les traitements trop agressifs avec les vieillards et de leur assurer une fin de vie paisible, en un mot de les mettre autant que possible à l'abri des chocs.

Second principe: un nombre croissant d'altérations apparaissent avec les années. Elles sont souvent compensées et peuvent devenir tout à fait latentes. Elles siègent au niveau de l'appareil moteur, de l'appareil cardiaque et dans le domaine de l'idéation.

Troisième principe: lorsque le choc frappe un sujet porteur d'un nombre critique d'altérations latentes, une désorganisation se fait jour, et le patient commence

à montrer des troubles évidents dans le domaine de la mémoire, ainsi que dans ses facultés de conception et de perception. Le facteur de désorganisation le plus commun chez les personnes âgées est le changement d'humeur, et celui-ci s'effectue le plus souvent dans le sens de la dépression. Certains de ces changements affectent purement le domaine de la perception et consistent essentiellement en une incapacité croissante à atteindre le contentement. La faute en est probablement due, en premier lieu, à une diminution du nombre et de la sensibilité des organes récepteurs. Elle conduit à une baisse de l'activité, et celle-ci, à sont tour, est entretenue par l'attitude née de notre civilisation, qui considère l'homme vieillissant comme un être de moins en moins capable d'action, et inapte à prendre la plus petite responsabilité. Cette manière d'envisager les choses mène à ce que nous avons qualifié de vieillissement prématuré, engendré par la civilisation. Il s'y superpose cependant bien vite une baisse de la capacité d'action, sur la base d'une atrophie par défaut d'usage. Si l'on arrive à rompre cette chaîne de facteurs interdépendants, il est parfois possible d'obtenir une restauration très satisfaisante de l'activité.

Le Tofrānil, dans certaines conditions, nous offre le moyen d'obtenir un tel résultat. Six cas nous le prouvent, qui ont pu être étudiés avec quelque détail. Notons, du reste, que cette thérapeutique a ses limites. Elle permet de contrôler une désorganisation par inhibition, qui a tendance à s'aggraver, mais elle ne peut rien contre une modification importante de l'humeur, qui est un facteur désorganisateur continuellement agissant.

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General discussion from the floor (summarized)

One participant brought to the attention of the meeting the occurrence of patients who manifested quite prematurely the stigmata of aging, women who look much older than their years, often with a premature menopause, affective symptoms and hypochondriasis — a syndrome one often sees among the aged but manifested here in early middle age. This syndrome is accompanied by subtle signs of endocrine deficiency. These people do not respond to ECT, but tend to respond with appropriate hormone treatment (ACTH, cortisone, stilbesterol and thyroid). Ten cases were cited. Dr. Cameron felt that perhaps these patients actually represented not a distinct entity but rather a normal variant in the population.

More discussion ensued as to the indications for Tofrānil, electroshock, and other modalities of therapy for depressive syndromes. One speaker raised the question whether some of the complications of Tofrānil are simply neurotic manifestations, i.e. indications that the patient has been forced to reorganize his personality defences in response to the effect of this drug on his neurophysiologic economy. This speaker wondered whether Tofrānil perhaps may actually change a so-called endogenous depression into a so-called neurotic depression.

In regard to side effects, another speaker mentioned that these can be influenced favorably by sympatholytic treatment. Further, the necessity for very close scrutiny by the physician in the case of ambulatory patients was underlined.

ELECTROENCEPHALOGRAPHIC AND BEHAVIORAL EFFECTS OF TOFRĀNIL

MAX FINK*

With the rapid increase in the number of potential psychopharmaceuticals, the need for screening technics has become more acute. In studies of the electrographic patterns of convulsive therapy, the hypothesis evolved that behavioral changes induced by new compounds could be related to their neurophysiologic effects as reflected by the type and degree of electrographic change (1, 2). This suggestion followed a similar one by Wikler (3) who stated that "regardless of the nature of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness." Studies with various psychotropics (4) and anticholinergic hallucinogens (5, 6) supported such a relationship. It is the purpose of this preliminary report to describe initial behavioral and electrographic observations with Tofrānil†, a new psychopharmaceutical, and to relate these observations to the neurophysiologic-adaptive hypothesis of the mode of action of physiodynamic therapies (1).

Methods

Two types of studies were undertaken in an open-ward, voluntary hospitalized population. In 28 acute experiments, consecutive patients referred for physiodynamic therapies were tested in the EEG laboratory at various stages of treatment. Tofrānil solution (10 mg/ml) was administered intravenously at a set rate (1 ml/40 sec.) until electrographic or behavioral changes became prominent, for a total of 40-125 mg (0.5-mg/kg). Behavioral observation and electrographic recording continued for one to three hours.

A second group of 16 patients manifesting depressive, withdrawn or retarded behavior were referred by their therapists for pharmacotherapy. The patients received daily oral Tofrānil, 75-250 mg. Behavioral observations and EEG recordings were made prior to and during treatment. Patients ranged in age from 17 to 58, and were diagnosed as suffering from schizophrenia, manic-depressive and involutional depressive psychoses, and psychoneuroses.

Observations

1. Acute Studies: On acute administration, there was an initial restlessness, associated with dizziness, dry mouth, "faintness," nausea, and on four occasions, vomiting. These symptoms persisted for 10-20 minutes, and were accompanied by lassitude, heaviness of the extremities and eventual drowsiness. Heart rate was unchanged or slowed. Subsequently, subjects were relaxed, quiet and disinclined to activity, even when returned to their ward.

The electrographic patterns accompanying these behavioral changes were initiated by a gradual decrease in voltages during the injection. By ten minutes, the per cent time alpha and mean alpha voltage had been halved. In four patients with moderate amounts of beta activity, such activity increased in voltage and per cent time. By twenty minutes, in association with behavioral lassitude, low voltage (to 50 microvolts) random theta frequencies (5-7 cps) appeared (Figures 1 and 2).

*Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, L.I., N.Y. Aided in part by grants M-927 and MY-2092 of the National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service; and by a grant from Geigy Pharmaceuticals. The technical assistance of Mrs. Hannah Mosquera in EEG recording is gratefully acknowledged.

†Trade Mark.

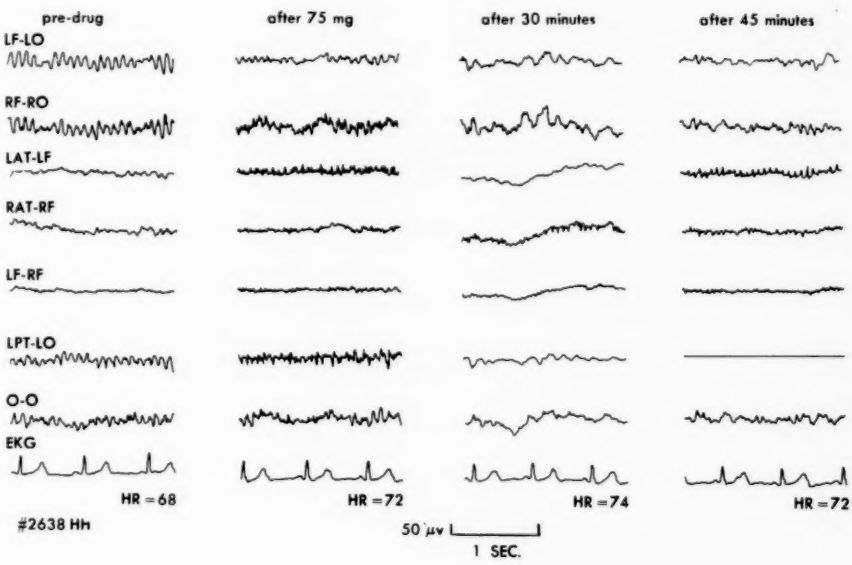

Fig. 1
Effect of intravenous Tofrānil on EEG delta
(female, aged 46)

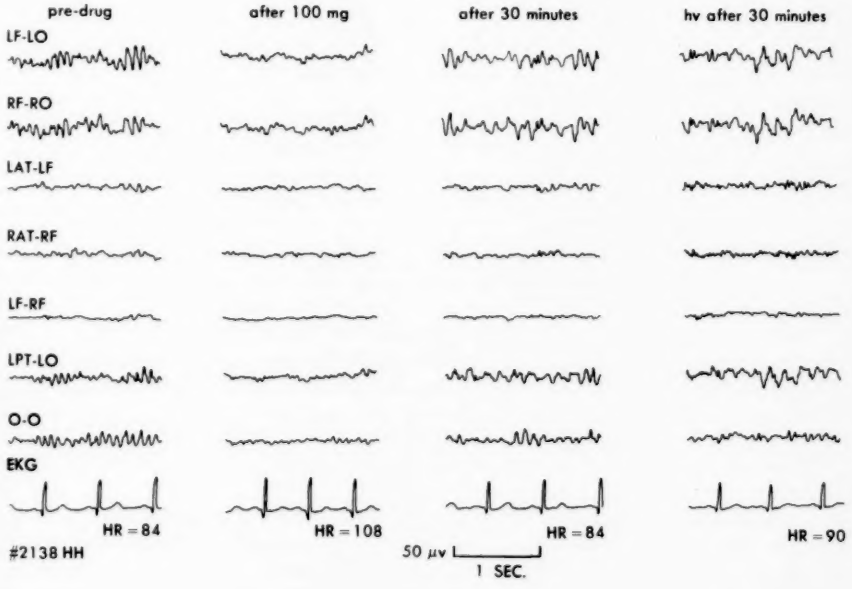

Fig. 2
Effect of intravenous Tofrānil on EEG delta
(male, aged 37)

In six records with post-convulsive delta activity, there was a marked decrease in voltages and per cent time of slow wave activity. These electrographic patterns persisted for half-an-hour to two hours (Figure 3).

There was considerable individual variability in the EEG response. In patients who received 100 mg or more of Tofrānil, EEG and behavioral changes were observed in all but three. In six patients, dosage of Tofrānil less than 50 mg were not associated with either EEG or behavioral changes.

2. Chronic Administration Studies: Sixteen patients, manifesting depressive symptoms with varying degrees of insomnia, anorexia, withdrawal, and agitation, have received Tofrānil medication for four weeks or longer. Medication was given in oral divided doses of 100-250 mg per day. Behavioral changes generally appeared during the second and were maximal during the third week of treatment.

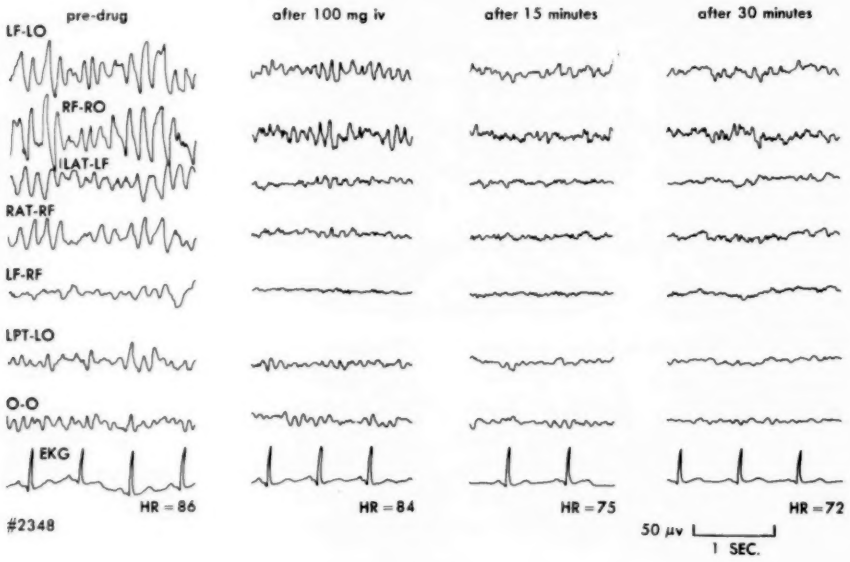

Fig. 3
Effect of Tofrānil on EEG delta
(female, aged 41: 24 hours post convulsion no. 7)

The most prominent behavioral adaptation was euphoric denial, which was noted in eight patients. The depressive attitude was no longer apparent. They participated more fully in ward activities, complained less of somatic symptoms, and denied, minimized or displaced their illness on inquiry. Agitation decreased, and complaints of insomnia became less. It became increasingly difficult to discuss significant life relationships as the patients pressed for an early discharge from the hospital.

In three patients somatization and restlessness increased and depressive affect persisted. In two of these, restlessness, insomnia and vomiting led to cessation of therapy. Sweating increased in most patients, but became a focus of attention in these subjects.

No change in symptoms were noted in five patients after four weeks of therapy.

While no serious complications of therapy were noted, nausea, increased sweating, vomiting, dryness of the mouth, restlessness and excitement, and increasing

insomnia were reported. These were prominent early in therapy, and except for the vomiting and restlessness, did not limit the treatment. In three subjects medication was initially administered parenterally without untoward effects. Abnormal motor patterns and seizures were not noted in these patients at these dosages.

Electrographic studies on chronic administration showed minimal changes. Voltages became lower and record modulation became poorer. Well-defined fast activity became more prominent, and in four subjects low-voltage theta (5-7 cps) activity was noted.

Discussion

These observations indicate that Tofrānil is an active central nervous system agent in man, both on oral and intravenous administration. The neurophysiologic effects are manifest electrographically as desynchronization of rhythms and a shift in frequency spectrum to the slower range. In depressed retarded subjects, Tofrānil administration is associated with such behavioral changes as decreased depressive affect with increased participation in ward activities, increased use of denial patterns (7) and occasional excitement.

In comparison to our previous experience with other physiodynamic therapies, the behavioral and electrographic patterns of Tofrānil are most like those seen with central anticholinergic agents. We observed desynchronization of frequencies, with an increase in theta activity, to be prominent with experimental anticholinergic compounds such as diethazine and benactyzine* (5, 6). In those studies, electrographic desynchronization was associated with behavioral alerting, excitement and illusory and hallucinatory activity. On Tofrānil administration, similar electrographic patterns of desynchronization were observed, accompanied by euphoria and increased ward participation. While we have not observed hallucinatory activity at our dosage ranges, Lehmann *et al.* (9) have reported hallucinations and hypomanic excitement in 7 of 84 patients receiving Tofrānil.

In earlier reports, Wikler (3, 10) suggested that the electrographic patterns of synchronization and desynchronization reflected neuron systems distinct from those neuron systems subserving such functions as 'sensation,' 'ideation' and 'level of awareness.' While these systems were frequently interlocked, dissociation between EEG pattern and behavior was observable under a variety of drug-induced states. In our earlier studies we were impressed that the electrographic and behavioral patterns seen after induced convulsions, anticholinergic compounds and phrenotropic agents were directly related. On acute administration of Tofrānil, however, electrographic desynchronization was associated with clinical sedation. These studies are consistent with Wikler's suggestion.

These observations permit the classification of the neuropharmacologic activity of Tofrānil in the central nervous system as predominantly anticholinergic. However, we have noted aspects of the electrographic and behavioral patterns reminiscent of increased cholinergic activity. These include the electrographic shift to slower frequencies and sedative, euphoriant behavioral effects. Such observations suggest that there may also be an effective degree of central cholinergic activity.

Summary

Intravenous administration of Tofrānil in 28 voluntary, open-ward psychiatric patients elicited electrographic patterns of desynchronization and an increase of theta rhythms, associated with behavioral alerting, relaxation and lassitude.

Chronic administration of oral Tofrānil in 16 depressed and retarded psychiatric subjects elicited behavioral adaptations of euphoric denial in eight, restlessness

*A recent report by Abood and Meduna (8) relates the behavioral improvement in depressed patients with JB-329, a new central anticholinergic agent which has similar electrographic patterns.

and somatization in three and no change in five. During the fifth week of administration, electrographic desynchronization was manifest.

It is concluded that Tofrānil is an active central nervous system agent, with a spectrum of activity most like experimental anticholinergic hallucinogens. The theoretic significance for neurophysiologic-behavioral constructs is briefly discussed.

Résumé

Nous avons étudié la relation existant entre les effets du Tofrānil sur le comportement et sur le tracé électrographique, chez des patients atteints de psychoses aiguës ou chroniques.

Méthode

Cas aigus: les patients retenus étaient examinés avant le traitement physiodynamique, ainsi qu'à divers stades de celui-ci. Le Tofrānil était administré en injections intraveineuses d'une solution à 10 mg/ml, jusqu'à un total de 40-125 mg (0,5-2,5 mg/kg), concurremment avec des examens électro-encéphalographiques.

Cas chroniques: des patients présentant de la dépression et un ralentissement du comportement étaient mis à la dose de 75-250 mg de Tofrānil par jour. Les examens encéphalographiques et du comportement étaient effectués avant le début du traitement, et à intervalles d'une semaine au cours de celui-ci.

Observations

1° Cas aigus

a) *Comportement:* au cours de l'administration du médicament, sur 28 cas, nous avons noté des nausées, des vertiges et de la faiblesse. Quatre fois des vomissements sont survenus. Le rythme cardiaque est demeuré inchangé, ou s'est ralenti. En 10 minutes ces symptômes diminuaient d'intensité et les patients se détendaient.

b) *Electro-encéphalogramme:* pendant le traitement, il y a eu une diminution du voltage dans toutes les fréquences. En 10 minutes le pourcentage de temps alpha baissait et les voltages tombaient à la moitié de leurs valeurs initiales. Chez les sujets à activité bêta (4 cas), celle-ci devenait plus importante. Au bout de 20 minutes, des ondes lentes de 5-7 cps, atteignant 50 microvolts, apparaissaient ici et là. Dans les enregistrements avec activité delta postconvulsive (6 cas) nous avons noté une baisse marquée des voltages et des pourcentages de temps dans l'activité des ondes lentes. Ces tracés électrographiques persistaient pendant ½-2 heures.

2° Cas chroniques

a) *Comportement:* seize sujets ont été observés à ce jour. Les effets initiaux de la médication furent des nausées, des vomissements, de l'agitation et de l'excitation, une exagération de l'insomnie et une transpiration très augmentée dont se plaignaient les malades. Le traitement a été interrompu dans deux cas avec agitation. Des 13 autres sujets, 6 ont vu leurs symptômes de dépression s'amender et ont pu reprendre une plus grande activité; ils ont pu être renvoyés chez eux, ou ont été prévus pour un prochain licenciement. Les autres n'ont guère présenté de changements dans leurs symptômes, ou n'ont été soumis à la thérapeutique que pendant un temps trop court.

b) *Electro-encéphalogramme:* Les enregistrements obtenus pendant le traitement n'ont montré que peu de modifications. Leur modulation était appauvrie et leurs voltages abaissés. Une activité rapide bien caractérisée a pris de l'importance; chez 4 malades nous avons noté une activité à bas voltage de 5-7 cps.

Conclusions

1° Chez les psychopathes, les effets électrographiques du Tofrānil sont une désynchronisation, suivie par une activité d'ondes lentes à bas voltage. Ces tracés sont moins prédominants dans les cas chroniques traités, et ressemblent alors à ceux que l'on obtient avec la benactyzine.

2° En ce qui concerne le comportement, nous constatons une augmentation de la motilité, un changement dans l'humeur et un malade plus éveillé.

3° Ces observations concordent avec les hypothèses neuro-physiologico-adaptatives expliquant le mode d'action des traitements physiodynamiques des psychoses.

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General discussion from the floor (summarized)

The question was asked whether administration of a large dose of Tofrānil once a day would not be as effective as multiple dosage. This would of course be a tremendous saving in the time of the nurses involved. In answer it was stated that Tofrānil is best given not in one large daily dose but in a series of small doses such as 2 tablets t.i.d. It was also brought out that Tofrānil has a tremendous influence on transference phenomena and that these can be analyzed in dreams and symbolisms. While such observations have been made, definitive results must await an extensive study.

Another discussant asked what is the difference between the effect of barbiturates and anticholinergic drugs on the EEG.

One discussant felt that the EEG was a poor tool, since it could be modified in only two ways, synchronization or desynchronization, and firm conclusions should not be drawn from such changes. He therefore felt that analogies between diethazine and Tofrānil were dubious and that nausea was not a specific effect of Tofrānil. He wondered if EEG changes would always exist in the absence of nausea, and felt it important to correlate EEG changes with clinical changes.

In replying to these comments, Dr. Fink stated that he considered Tofrānil an anticholinergic drug because of its similarity to other anticholinergic drugs in regard to its EEG patterns. Dr. Fink recalled that Dr. Sigg's paper had also indicated that Tofrānil was an anticholinergic drug. Many anticholinergic compounds appear to have rather specific central effects, and some are also experimental hallucinogens. In his experience, barbiturates produce not desynchronization, but rather synchronization. This becomes clear if the factors of dosage and time are considered. Thus the initial effect is hypersynchronization; if the drug is continued, sleep is of course produced and the initial effect disappears.

The author replied to the criticism of his use of EEG. He agreed that it is a poor tool in many respects, but that it is possible to analyze EEG records for synchronization, desynchronization and frequency shifts. One obtains different patterns with different agents even in the same patient. Dr. Fink explained that he was making a long-term study, and hoped that more conclusive data could be offered at a later time.

PSYCHODYNAMIC ALTERATIONS CONCOMITANT WITH TOFRĀNIL ADMINISTRATION

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The introduction of Tofrānil† in the treatment of depressed patients (1, 2) and further trials with this substance (3, 4) indicated its relatively specific effect on the mood state of depression. This observation led to the conclusion that due to the specific dynamic constellation involved in depressive states, here was a situation par excellence to explore the organo-dynamic relatedness of a chemical substance and a dynamic state. In previous investigations with other pharmacological substances (5, 6, 7, 8) it was submitted that correlative psychodynamic studies during pharmacotherapy are useful and necessary to provide rationale or clues for the future application of drugs in psychoanalytic and psychotherapeutic situations. The purpose of the present paper is to report on the alteration of the psychic structure concomitant with Tofrānil administration in depressive states and to reach a theoretical formulation in regard to the mode of action of this substance.

Methodology

The general methodology used in psychodynamic studies during pharmacotherapy has been discussed previously (8, 9). It will be discussed briefly here under the headings of patients, the regime of drug administration, the collection of observations, the sectors of observations and the criteria of assessment of change.

1. Patients.

Twelve patients were used in this study. The common denominator of their psychopathology at the time of drug administration was a depressive state. There were 6 males and 6 females with an average age of 35 years. Diagnostically they consisted of 2 manic-depressive patients in depressive phase (psychotic depression), 5 neurotic depressive patients, one alcoholic, one schizophrenic and 3 character disorders. The latter three patients, who originally had come for an understanding of their character difficulties (homosexual anxiety, general libidinal and aggressive inhibition, and anxiety over piano-playing in a professional pianist respectively) were given Tofrānil on a research basis, because during their psychoanalytic psychotherapy they developed mild depressive states due to a regression to the depressive position. The schizophrenic patient was treated with Tofrānil because his main symptomatology, which was withdrawal and splitting, was seen as a regressive defense against an overwhelming depressive feeling over the death of his fiancée. This patient had experienced mourning only for a very short time, followed by a gradual withdrawal and retreat from object-relations with increasing apathy and lack of feeling. The alcoholic patient was treated with Tofrānil because his alcohol intake was an evident attempt to overcome emerging depressed feelings. This patient's alcoholism was intermittent: the intake was impulsive and rapid until the patient reached relief.

2. Regime of drug administration.

Tofrānil was administered orally with an average dose of 75 mg. The routine in 9 patients, where the drug was used in a uni-blind way, consisted of starting the patients on 75 mg daily, and increasing the drug to 150 mg by the second and to 200 mg by the third week if no therapeutic response occurred. In no case was it necessary to go beyond 200 mg daily. The duration of this treatment ranged from

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3 to 9 months in 7 patients. In two psychotic depressions a hypomanic state developed within three weeks, necessitating the discontinuation of Tofrānil and resumption of chlorpromazine therapy.

In three patients who were in intensive psychotherapy Tofrānil was used in a double blind regime of multiple drug administration, with a dosage of 100 mg daily. These patients were part of a larger psychopharmacological study with 3 other drugs used in a double blind way. Tofrānil was included once in this schema, in two patients for a period of 10 sessions and 3 times in the other patient, for a period of 3 sessions each, for a period of time encompassing 10 sessions. One objective was to compare the changes occurring in dynamic sectors of observations, as described below, concomitant with Tofrānil and the other 3 drugs.

3. Collection of observations.

The data upon which the results and theoretical formulations of the paper are based were collected in two interview situations.

(1) Supportive situation.—This consisted mainly of observing the patient and recording his associations. It is called supportive because no uncovering of unconscious processes was attempted. Its sole aim was the detection of change. The technical rules adhered to consisted of: (*a*) withholding of interpretation and explanation in order to prevent, as much as possible, the contamination of the emerging psychic process, and (*b*) encouragement of free association. These were either tape recorded or noted verbatim during the session. From this material a phenomenological appraisal of the changes of depressive states was made. The inferences about the underlying dynamic changes were based upon these phenomenological alterations.

The patients were seen for an average of 2 times weekly, with the sessions lasting from 20 to 45 minutes, until the disappearance of depression. They were followed afterwards at long intervals.

(2) Analytic situation.—This consisted of the setting of psychoanalytic psychotherapy, which was applied to only 3 of the patients as mentioned previously. The patients were seen in weekly sessions of 50 minutes for an average of three sessions. They had agreed beforehand about the research project, and were told that they would receive drugs. The therapist was ignorant of the nature of the drugs, and knew only that they were harmless. In order to increase the reliability of the criteria of assessment of change (see below) the matter of drug administration was handled as casually as possible, with a minimum of emphasis on the drug. The therapist did not inquire about the effect of the drug unless the patient spontaneously talked about it. The therapist took detailed notes of significant sequence and content of association immediately after the termination of the sessions.

4. Sectors of observations.

Particular emphasis was put upon classifying data according to 4 sectors of observations, as described elsewhere: the organization of mood, of ego, of drives and of object-relations.

The organization of mood was considered under 4 states: depression, elation, anxiety and indifference. The mood was considered as a crucial index indicating an energetic shift or an economical alteration in the psychic apparatus.

The organization of ego was considered under its defensive and executant function. In the present study an attempt was made to gather evidence indicating alterations of defenses considered specific for depression, e.g. introjection. The organization of drives was considered under the dialectic of libidinal and aggressive

tendencies, and an attempt was made to determine the most immediate changes in these drives.

The organization of object-relations was considered under its external and internal aspects. An attempt was made to clarify the shift in the energetic investment of inner and outer happenings (inner and outer object-relations). The theoretical guide was the psychoanalytic conception of depressive states in which the point of emphasis is the internal objects system of control (super-ego components).

It should be noted that the above divisions were adhered to with full knowledge of their close relatedness and their separation for analytic-descriptive purposes.

5. Criteria of assessment of change.

One of the decisive problems of psychodynamic studies in connection with drug administration is how to be certain that a given change in psychodynamic states is due to the specific effect of a given drug and not the symbolic significance of an oral intake, or to transference phenomena. The author (7, 9) has proposed the following criteria, which were used in the present study, to determine the psychopharmacological validity of a change.

(1) The patient should be taken as his own control and studied longitudinally. This study, by giving the observer an adequate knowledge of the patient's habitual mode of behaviour, patterns of defense and object-relations, and in general of his inner world, will allow him to detect a change with a certain degree of reliability. Only such an observer with adequate insight into his counter-transference states, which play a crucial role in his opinion of the patient as a datum of research, can give a statement about the occurrence of a change.

(2) The above observer can use two closely related criteria to reach a relative certitude about the psychopharmacological validity of the change. These criteria are two qualities of "emergence" and "incomprehensibility". A dynamic event cannot be taken as due to the effect of a drug unless it appears "emergent" in the on-going psychic processes, which are under the scrutiny of the observer. Such an event cannot be emergent unless it is "incomprehensible" to the observer in connection with what he knows about the patient's on-going reactivity and what has preceded its appearance. It is for this reason that we have suggested that the true state of affairs in psychodynamic studies during pharmacotherapy cannot be reached unless the patient is undergoing an intensive psychotherapy which allows the therapist a detailed knowledge of the patient's internal reality.

(3) Control observer.—This consists of an independent observer, with the same frame of reference as the principal observer (the therapist), who goes over the data obtained from the patient, reaches his conclusions and then compares them with those of the principal observer. Agreement of these conclusions gives a greater degree of reliability to the final assessment. However, a disagreement does not rule out the contentions of the principal observer because he possesses those non-reportable cues and indices from which to infer the changes in the qualitative and intangible phenomena of the mind, which can be procured only by close contact with the patient. The control observer lacks such cues.

This brings up the matter of reliability of the principal observer's observation. It is submitted that an observer with a minimum of countertransference or with the capacity of perpetual analysis of countertransference and an adequate degree of adaptation and sincerity remains the most reliable detector of change in studies pertaining to psychodynamic states of the mind.

Results

These will be presented under 4 headings: the organization of mood, of drives, of ego, and of object-relations. These different headings will be presented separately with the explicit knowledge of the arbitrariness of many points of separation. The

mood is added to the three parameters of psychic structure because it is felt that (1) it represents the core of the problem under inquiry, i.e. depression; and (2) it is the experiential state, indicative of economical shifts in the mind (in the psychoanalytic sense).

1. Organization of mood.

There was a definite reduction of depressive feeling in all patients manifesting overt depression in the supportive category. The change in depression was manifested phenomenologically as the experience of acceleration of time, mobility of spatial boundaries and an openness to the world ("I feel the time goes faster, the day passes now more quickly;" "I feel that I would like to go out, to reach out, to expand my activities;" "I need more outlets"). This experiential state evidently was related to the changes in the distribution of drives and modifications of object-relations.

In two patients with depressive states of a manic-depressive psychopathology, the depression was lifted and within 3 weeks changed into elation, which then gradually developed into a frank manic state in one patient and into a hypomanic state in the other. This was consistent with our previously reported observations. Both patients' manic state could be effectively controlled with chlorpromazine. These two patients had not shown in the past such a rapid mood swing, and it could be stated that Tofrānil had accelerated the shift from depression to mania.

Of three neurotic patients in psychoanalytic psychotherapy, one showed relief from the depression, one experienced a marked degree of anxiety related to the emergence of aggressive impulses (see below) and one did not change. This latter patient showed no change in any aspect of his psychic structure during Tofrānil treatment which could be termed emergent. This was conceptualized as due to the low intensity of the patient's depression, which was quite mild. This contention is in agreement with what was noted in the previous studies on larger numbers of patients (4, 10) where it was observed that unless the depression is at a certain intensity Tofrānil has no particular effect. Tofrānil does not seem to alter the so-called "normal" or "within normal range" depressions.

The response of one schizophrenic patient in this series posed an interesting theoretical problem. As was noted before, he was given Tofrānil because his withdrawal and his partial mutism were seen as a regressive defense against an overwhelming depression, a pathological mourning over the death of his fiancée. He had failed to respond previously to several other drugs, including phenothiazines. Within a week after the start of Tofrānil he stated: "I feel much better; I am not better totally, but I feel this movement." His withdrawal decreased, he began to speak to the members of his family and he started to "suffer from my condition." His family noted that previously he had never told them about his sufferings. Another paranoid schizophrenic, not reported here, whose condition was clearly seen as a regressive defense against depression, also responded favorably to Tofrānil. His response was more marked than that of the patient described in this series and resulted in a marked improvement in his condition.

These two cases confirmed the general impression that Tofrānil seems to influence specifically the depressive core, that intensity which is experientially referable as an overwhelming pressure from the controlling system of the mind (super-ego components) to the self.

2. Organization of drives.

In general there was a primary reorganization of aggressive drives and a secondary reorganization of libidinal drives. Aggressive impulses seemed to begin to be directed outwardly. There was a shift of aggressive cathexis from inner to outer objects. This was manifested in a general feeling of "I want to do more;"

"I feel more active;" "I seem to be able to tell people off;" "I can defend myself now, I don't shy away any more."

In two instances the exteriorization of aggressive object-relations was quite intense. The first patient, a man of about 35 years who had been suffering for years from a mild feeling of depression and inferiority feeling, was given Tofrānil due to the exacerbation of his depressive symptomatology. Previously he had taken many drugs with no effect. He had a high intelligence and was a reliable introspectionist. Within a week he experienced to his amazement a "transformation in my relations to other people. I am concerned that I might hit somebody. I told my father off the other day, I am arguing like mad. I feel like something sudden had happened to me." He started to take on new responsibilities, enrolled in night courses and on occasion felt "triumphant" (a mild hypomania).

In another patient the shift of aggressive investment was more decisively demonstrated. This 40-year-old female had come for psychotherapy because of a life-long history of aggressive and libidinal inhibition. She was quite unhappy about her restricted and inhibited existence. In the first 6 months of psychotherapy during 2 sessions she experienced certain internal happenings, which could be clearly related to the emergence of anger. In one of these sessions she had been waiting for an hour before coming in because she had "forgotten" the exact time of her appointment. All the associations were indirectly indicative of her anger at not having been received sooner by the therapist ("if you really liked me you could have changed your time"). However, she did not experience any anger. After interpretation of this, she "felt fidgety," "I feel like screaming . . . I feel nervous." Further associations made it possible to make her realize her repressed anger. Then she said, "I have noticed that whenever I feel angry, or want to scream I am angry, my whole body feels as if distended, it feels like something is pushing out, as if I am going to jump out of my skin."

A few months afterwards she developed a state of marked anxiety and depression consequent on a temporary absence of the therapist. It could be seen that this was a repetition of a childhood depressive episode subsequent to the death of her mother in a car accident. The patient was mourning for the therapist, whom she had in fantasy destroyed, as she once had done with her mother. She was put three times on Tofrānil. Each time within 3 days she developed a marked increase in anxiety and feelings identical to the above-mentioned session. She felt "as if I am going to jump out of my skin . . . something inside is pushing. I come to the point of screaming." Later, after some aspects of her "mourning" over her ambivalence towards the therapist had been uncovered, her death wishes against the therapist came out rather suddenly. In the session she regressed temporarily to a paranoid state: "sometimes I feel afraid to do something . . . like hitting . . . I wanted almost to hit, to ki . . . (she left unfinished the term "kill"), God, what did I say . . . (long pause) these nurses. I was telling you yesterday, they bother me, I am afraid to say anything, they are like guards," etc.

It should be noted that these three trials with Tofrānil were deliberate and the patient was unaware of the nature of the drug. The identical responses from the point of view of time and content and their emergent quality favored their relatedness to Tofrānil. In this patient the intensity of the emergence of aggression was responsible for its disorganizing effect and the fact that, unlike other patients whose depression decreased, she could not tolerate this inner shift of aggression so that the drug had to be discontinued.

Libidinal drives seemed to be only secondarily affected. The reorganization of the patients' love attitudes and genital activities occurred after the reorganization of aggressive impulses. This was noted particularly in 4 patients who complained of marked loss of interest in sexual relations concomitant with the onset of depres-

sion. This interest began to return many weeks after the depressive state had subsided and patients had resumed their social and domestic activities. One patient demonstrated this continuity by saying, "I feel pretty good now, I can stand up to my husband and say things without getting upset, but as yet I am not sexually interested in him as much as I was before my depression."

3. Organization of the ego.

In this connection an attempt was made to determine the alterations of defensive functions of the ego, particularly the introjection mechanism which seems to be the main defensive process in depressive states. This defense appeared to be at least partially altered in 10 patients. This was based upon inference from the following observations: ability to express aggression outwardly, decrease in guilt feelings (see below), the disappearance of the need to "take in" alcohol in the alcoholic patient and in two patients a change from depressive and oral associations during the session, to anal (obsessive-compulsive) associations. A brief account of one of these patients will illustrate this. This patient, a single man of 29 years of age, had come for psychoanalytic psychotherapy with the main complaint of marked anxiety while playing the piano, which was his profession. After 6 months of therapy he became moderately depressed, after it was uncovered that his desire to play the piano to be a "great musician" was a defense against marked feelings of inadequacy and the fact that he was an "ordinary" pianist with little talent. This narcissistic injury was perceived as a great loss and he began to feel depressed gradually. He was put on Tofrānil for the sole purpose of detecting a change, as mentioned before. For three sessions all his associations were depressive. He was preoccupied with fantasied lost object relations: "I am worried that I have not really any talent . . . I am going to lose my career. I won't be able to play the piano . . . how am I going to make a living? I got so worked up that I thought I won't be able to make a living and I will starve." Also he brought out many self-deprecating tendencies. He was convinced that "I have no talent, that I won't be able to manage. I have no diplomas, and I am almost 30 years of age", etc. He continued this way for five sessions and then rather suddenly started to feel a lifting of this depressive feeling, without any definite indication in the psychotherapeutic process to make this change comprehensible, i.e. the change in the unfolding of psychic processes seemed emergent. His associations were controlled ("held back") about "taking in", with homosexual associations leading to prostitution fantasies, i.e. he wished to let himself be penetrated in order to obtain money. He was concerned no longer about lost objects, but only to keep whatever he had. These were conceptualized as anal modes of object relations. A change from depressive-oral associations to obsessive-compulsive anal associations seemed to have occurred.

4. Organization of object-relations.

In general there was a change from preoccupation with the inner world and internal happenings (internal object relations) to the outer world and external happenings (external object relations). This change was obviously connected with others mentioned previously and its quality was in line with the change in the direction of aggressive impulses. The evidence for the change in object-relations was the following: (*a*) Disappearance of guilt feelings. This connotes a change from painful preoccupations with one's own world ("I am bad") and perpetual relating and associating to one's own super-ego, to a more adequate involvement with the outer world and a feeling of worthiness ("I am no longer sitting there wrapped up in myself and constantly thinking about what is going on in me; I can go out now, talk to people, do things, and even get mad at my husband"). (*b*) Disappearance of self-destructive tendencies. This is closely connected to the disappearance of guilt feelings (suicide being in one of its dynamic aspects the culminating point

of guilt and redemption of it) and the direction of aggressive investment. This investment reverses itself and instead of involving the inner world and the self, returns to the outer world. This reversal is usually organized. In one patient this appeared in form of a desire to hurt and "shoot out-doors" (instead of in-doors). (*c*) Disappearance or decrease in hypochondriacal symptoms. Patients were no longer preoccupied with their bodies and bodily functions. Concomitant with Tofrānil treatment they began to be interested in outer bodies and objects. One patient was incessantly preoccupied with different pills she was taking. She perpetually talked about them, as though they were not only parts of her body, but things inside her body. Under Tofrānil this overconcern with literally internal objects decreased considerably, the patient stopped talking about the pills and could divert her interests to things in the environment. (*d*) Increase in concentration, initiative and "outgoingness." Ability to read, to write, to get involved in different tasks for longer and longer periods was one of the first overt changes in object-relations noted in depressed patients receiving Tofrānil. The individual became capable of "becoming interested in what goes on in the world," as one patient said. Another patient (a highly sophisticated intelligent executive) pinpointed this "return to the world" by stating, "before I had difficulty in being in the world — to be present; now I can be present in the world, in here."

Discussion and Conclusion

From the aforementioned considerations it can be summarized that concomitant with Tofrānil administration the following events seem to occur: (1) a decrease in the mood of depression and in some instances a change to elation and manic mood; (2) a change in the direction of aggressive drives from inward to outward; (3) a secondary reorganization of libidinal tendencies; (4) a decrease in guilt feelings and a change from preoccupation with internal object-relations to external object-relations; (5) a decrease in the need for alcohol intake.

The theoretical problem is how to relate these changes in order to reach an understanding about the mode of action of Tofrānil in depressive states. It is submitted that the psychoanalytic framework contains adequate concepts to deal with this problem, and that these can be found in the economic principles of the mind. In a general and tentative way it is contended that concomitant with Tofrānil administration an economic shift, a change in the energetics of the mind occurs, with its point of emphasis on the internalized objects system of control or imago percepts (super-ego components). In depression these percepts and these components are the central core of the inner conflicts. The individual seems to suffer from a super-ego over-invested and over-charged with harshness and aggression. Tofrānil seems to produce a decrease in this super-ego harshness and overemphasis. This can be conceptualized as a decrease in aggressive investment of super-ego components, or controlling internal objects. Thus considered, all 5 points mentioned above become comprehensible as the consequence of a unitary process. The disappearance of the need for alcohol intake, which was observed also in some other patients not reported here, can be explained in the same manner if we consider the dynamic similarity between depression and addiction, and the role of the super-ego in both conditions.

Three points are in favor of an economic shift rather than a structural change: (1) the necessity for the existence of a certain intensity of depression; unless this intensity is relatively high Tofrānil has no appreciable effect; (2) the possibility of relapse not only in those in whom the drug is discontinued early, but in some patients who are still on the drug; and (3) the possibility of a shift from depression to a manic state in patients who originally manifested a proneness to mood swing and sporadic over- or under-emphasis of the super-ego, i.e. manic-depressive

patients. Theoretically this can be predicted from what was said about a gradual de-investment or de-cathexis of super-ego components concomitant with Tofrānil intake. If this de-investment continues, a point will finally be reached where the super-ego structure will be depleted of some of its intensity and will lead to a hypomanic and manic state, particularly in those individuals who basically are prone to such shifts.

As we have repeatedly noted before, the economic principle of the mind (in the psychoanalytic sense) is the principle most suited to explanatory inquiries into pharmacotherapy, because this principle contains the concept of psychic energy. This concept in turn involves the concepts of drives, which have an organic source and can thus be influenced by organic substances. This principle is more suitable in pharmacotherapy because it assumes the shiftable, displaceable nature of the hypothetical psychic energy, or rather "intensity," which corresponds to the transitory nature of the results of pharmacotherapy. Another concept such as that of the "memory trace," which assumes neuronal alterations, is unsuitable because if a memory trace is changed the resultant state would be permanent.

It is submitted that the tentative acceptance of energetic shifts in super-ego components concomitant with Tofrānil intake brings into harmony other aspects of the psychopharmacology of manic-depressive states. One of these aspects which to the writer seems worthy of note is the comparison of three features of Tofrānil with the effect of phenothiazines on manic states. The evidence can be summarized in the following way: (1) the indication par excellence of phenothiazine compounds has been and is the manic state; it is here that a "cure" of a psychiatric syndrome — even though temporary — is accomplished; (2) in instances of labile mood swings and rapid manic-depressive mood shifts, too long or too intense phenothiazine administration may shift the mood from elation to depression; (3) the indication par excellence of iminodibenzyl compounds (here Tofrānil) is the depressive state; (4) in instances of rapid manic-depressive mood shifts, Tofrānil administration for too long may shift the mood from depression to elation; (5) the administration of iminodibenzyl in case 2 and phenothiazine in case 4 can reverse the process of mood organization; (6) mania and depression are dynamically similar in that the point of emphasis of the conflicts resides in the super-ego; (7) pharmacologically, phenothiazine and iminodibenzyl are related in that their chemical structure is closely similar.

If one allows some speculation it can be seen that for the first time in the field of psychopharmacological correlation there are two substances quite similar in their basic chemical structure which have a marked influence on two clinical states quite similar in their basic dynamic structure. If the naiveté of the inference from an epistemological point of view were not so striking, one might ask: has this basic chemical structure some affinity or relatedness to neuronal patterns or organizations in connection with the internal objects system of control (super-ego elements) or their energetic investment and pathways?

Before closing it may be worthy of note that observations presented here and psychopharmacological data in general bring confirmatory evidence of the usefulness of the concept of psychic energy as it is elaborated in Freud's writings, in both his earlier "closed system" hydraulic model and his later "open system" structural field model (11) which are essentially akin from the energy point of view.

Summary

The purpose of this paper is to report on the alterations of psychic structure concomitant with Tofrānil administration in depressive states, and to reach a theoretical formulation in regard to the mode of action of this substance.

The methodology consisted of intensive psychodynamic investigation of 12 patients in whom depression was seen as a major component of their psychopathology.

The data were obtained from two different interview situations: supportive and uncovering psychotherapy. Nine patients were seen in a supportive psychotherapeutic situation, consisting of one to two weekly interviews. The sole aim was the recording of phenomenological changes. Three patients were seen in an intensive psychotherapeutic situation during which Tofrānil was administered as part of a larger double blind psychopharmacological study and solely for the detection of change in dynamic sequences.

The analysis of data revealed the following alterations: (1) a decrease in the mood of depression and in some instances a change to elation and manic mood; (2) a change in the direction of aggressive drives from inward to outward; (3) a secondary reorganization of libidinal tendencies; (4) a decrease in guilt feelings and a change from preoccupation with internal object-relations to external object-relations; (5) a decrease in the need for alcohol intake.

On the basis of the above observations it was conceptualized in the psychodynamic framework that under Tofrānil administration an economic shift in the aggressive cathecting energies of super-ego components (internalized objects system of control or imago percepts) of the psyche occurs, resulting in a primary reorganization of aggressive investment of inner and outer objects, a secondary reorganization of libidinal investments, and a relief of depressive state. This shift in the economic balance seems to be transitory and necessitates a certain intensity of depressive feelings.

Résumé

Le but de ce travail est de relater les modifications de la structure du psychisme survenant lors de l'administration de Tofrānil au cours des états dépressifs, et de rechercher une expression théorique expliquant le mode d'action de cette substance.

Notre méthode a consisté en une exploration psychodynamique poussée de 12 sujets, chez lesquels la dépression était considérée comme une composante majeure de leur état psychopathologique.

Les données ont été obtenues par deux procédés différents: psychothérapie de soutien et psychothérapie analytique. Huit patients ont été examinés en psychothérapie de soutien, consistant en un ou deux entretiens par semaine, ne visant qu'à consigner les modifications phénoménologiques. Trois autres patients ont été soumis à une psychothérapie intensive, au cours de laquelle le Tofrānil n'était administré que dans le but de détecter les changements apparaissant dans les séquences dynamiques sous son influence.

L'observation a été centrée sur quatre secteurs de la structure psychique, soit l'organisation du moi, ainsi que celles des pulsions, des relations objectales et de l'humeur. Cette dernière a été particulièrement étudiée, en tant qu'indicateur par excellence des modifications de l'équilibre psychodynamique.

L'analyse des résultats révèle les altérations suivantes: 1° un changement des préoccupations, qui passent de l'intérieur à l'extérieur; 2° une diminution du sentiment de culpabilité; 3° une orientation différente des pulsions agressives, et dans certains cas leur libération sous forme d'explosion agressive; 4° une réorganisation secondaire de l'investissement libidinal; 5° l'aspect euphorique et hypomaniaque de patients classés comme maniaco-dépressifs; 6° une certaine intensité de la dépression est nécessaire à l'obtention de ces effets; les légères modifications dépressives de l'habitus ne sont pas influencées par le Tofrānil; 7° un besoin diminué de boissons alcooliques; 8° un changement portant uniquement sur

l'état dépressif; 9° aucune modification des caractéristiques de base de la personnalité, antérieures à l'état dépressif.

Sur la base des observations ci-dessus, l'auteur a mis en évidence une mutation de l'équilibre dans les impulsions agressives des composantes du super-ego du psychisme (système de contrôle des objets internalisés, ou perception des imagos). Il en résulte une réorganisation primaire de l'investissement agressif, une réorganisation secondaire de l'investissement libidinal, et une sédation dans l'état dépressif. Ce changement dans l'équilibre psychodynamique semble transitoire, et nécessite, pour se produire, une certaine intensité de l'état dépressif.

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HUMORAL CHANGES PRODUCED BY TOFRĀNIL AND PHENOTHIAZINE COMPOUNDS*

H. HIPPIUS**

About 30 years ago the German psychiatrist Reichardt put forward the thesis that all noxious influences affecting the primitive brain stem can initiate psychic symptoms relating to the motor extra-pyramidal and autonomic systems (1). Symptoms starting in these three functional regions can also arise during neuroleptic therapy with phenothiazines and with reserpine. From this familiar clinical grouping of symptoms the conclusion can already be drawn that neuroleptics exert their activity on the brain stem (2). The psychic and motor extra-pyramidal effects of neuroleptic therapy have been much investigated in recent years. The autonomic actions have for the most part received less attention or have been dismissed as unpleasant side effects. However, they certainly belong just as much as the motor extra-pyramidal symptoms to the complete picture of the way in which neuroleptics exert their effect.

Arising from the interest in our hospital in the investigation of these neurovegetative effects (3), I have been endeavoring since 1953 with Selbach and Kanig (4-7) to obtain a clear understanding of these vegetative effects of neuroleptic therapy by means of humoral studies. We make the following examinations at regular intervals in our patients before and during clinical treatment:

1. Red-cell counts
2. White-cell counts
3. Determination of serum protein fractions
4. Determination of total serum protein
5. Determination of alkaline phosphatase activity of the serum

In comparative investigations with the phenothiazine derivatives chlorpromazine, mepazine and perazine, we found that the course followed was similar to that with reserpine. Thus the clinical similarity between the action of the phenothiazine derivatives and of reserpine in schizophrenics has a parallel in the similarity of the biochemical changes during the course of treatment.

At this stage it was clearly of interest to carry out similar studies during treatment with Tofrānil†, which had been at our disposal for nearly two years. Our clinical experience with 118 patients (8) shows us to be in agreement with most other workers in that although Tofrānil is related chemically to the phenothiazines it is less effective in the schizophrenic syndrome than in the depression syndrome. There are thus significant differences in the psychic effects of Tofrānil and the phenothiazines, and our further studies were designed to show whether these marked therapeutic differences were paralleled in the vegetative sphere or not.

From among all the patients undergoing Tofrānil therapy in our hospital we selected a group of 25 with either endogenous depressive phases or the involutional depressions. The means of each set of observations were plotted to show the course of the changes, and the curves for Tofrānil compared with those obtained with chlorpromazine. The following differences were especially noteworthy:

1. During several weeks treatment with Tofrānil, alkaline phosphatase showed a transient but statistically significant increase compared with a normal group. A similar result was obtained with schizophrenics during treatment with chlorpromazine (see Fig. 1).

2. Of the changes in the serum protein fractions, those of the α_2- and β-globulins were particularly striking. Before treatment the concentrations of both fractions

*Translation.
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†Trade Mark.

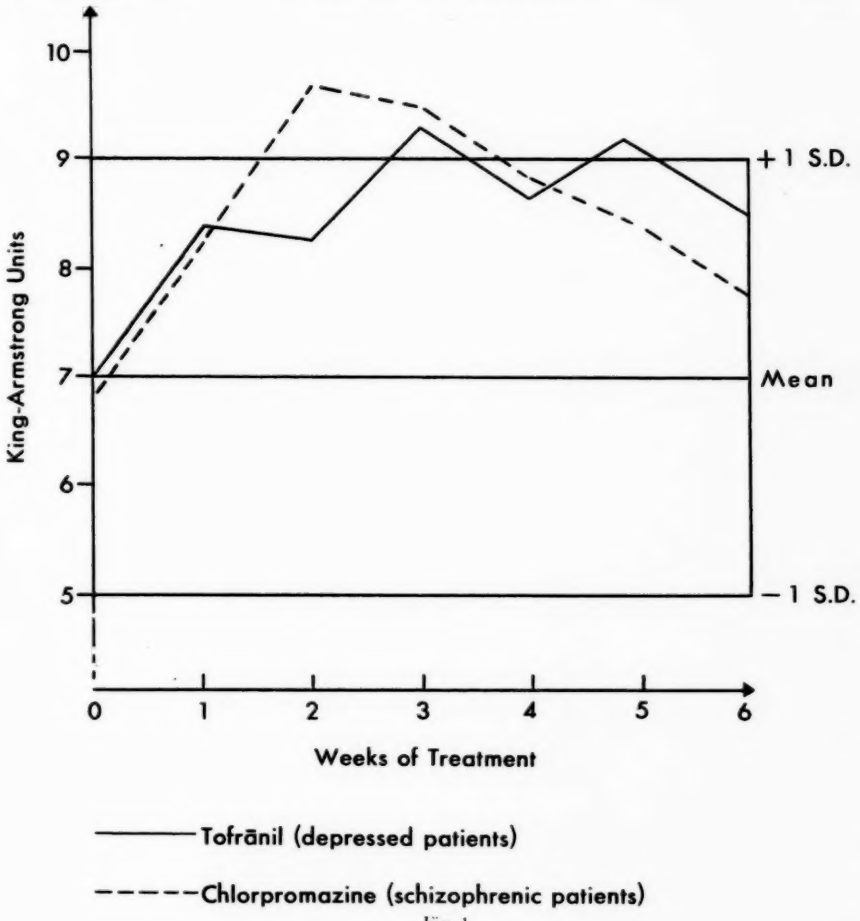

Fig. 1
Alkaline serum phosphatase

in the group with depression lay within the mean variance of the values found in healthy subjects. In the group with schizophrenic psychoses on the other hand, the mean α_2- and β-globulin concentrations were significantly higher than normal.

During treatment with chlorpromazine the initially high concentrations become normal. During Tofrānil treatment transient but statistically significant increases occur during the first weeks of treatment; however, the values become normal again during the course of further treatment. Although the initial values for the patients in the schizophrenic and depression groups are not comparable, it is nevertheless clear that both chlorpromazine and Tofrānil have a regulatory action on serum proteins and in particular on the α_2- and β-globulins (see Fig. 2).

3. During treatment with Tofrānil, as also with chlorpromazine, there is a statistically significant increase of eosinophils followed by a decrease later in the course of treatment. The transient changes in eosinophils in the Tofrānil group correspond fairly closely with those observed during perazine therapy; during chlorpromazine treatment the increase in eosinophils is not only much more marked but also starts earlier (see Fig. 3). With both phenothiazine derivatives and Tofrānil

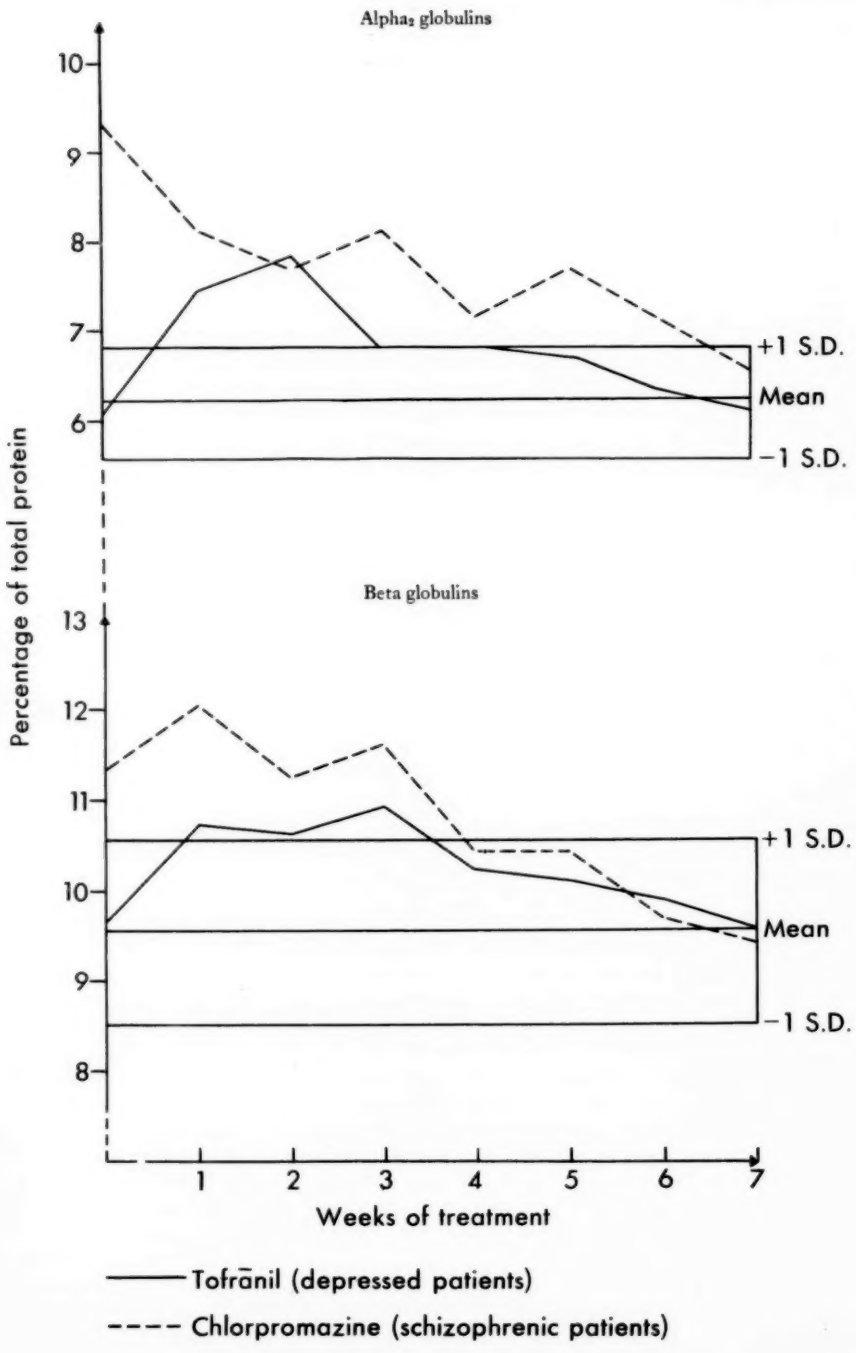
Alpha2 globulins
10
9
8
7
6
+1 S.D.
Mean
−1 S.D.
Percentage of total protein
Beta globulins
13
12
11
10
9
8
+1 S.D.
Mean
−1 S.D.
1
2
3
4
5
6
7
Weeks of treatment
Tofranil (depressed patients)
Chlorpromazine (schizophrenic patients)

Fig. 2

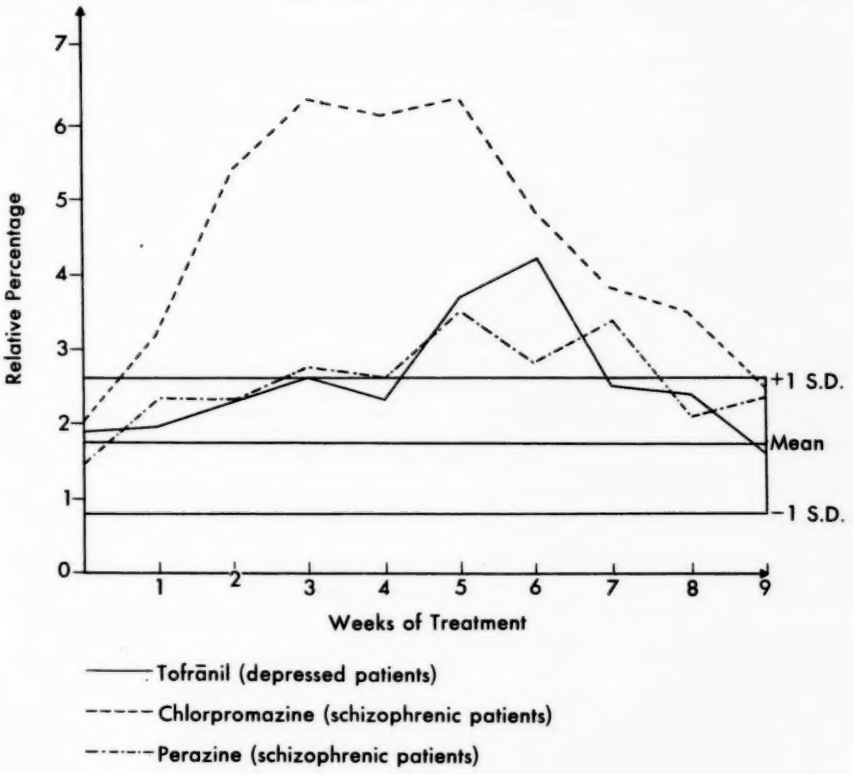

Fig. 3
Eosinophils

the eosinophil peaks are followed by increases in the monocytes. However, these are not statistically significant.

As to the conclusions which may be drawn from these humoral studies, it is evident that Tofrānil treatment causes biochemical and vegetative changes similar to those caused by the various phenothiazine derivatives and reserpine. In our opinion this indicates that Tofrānil too has an action on the brain stem and that this is the reason for its psychotherapeutic effect.

The similarity in the site of action of the phenothiazines and Tofrānil is not inconsistent with the clinical observation that phenothiazines are mainly effective in schizophrenic syndromes and Tofrānil in depression syndromes.

Résumé

En psychiatrie clinique, le Tofrānil — dérivé de l'iminodibenzyle — se différencie nettement des préparations à base de phénothiazine, malgré sa proche parenté chimique avec la chlorpromazine. Alors que les dérivés de la phénothiazine influencent favorablement les psychoses à caractère schizoïde, le Tofrānil agit essentiellement sur le syndrome dépressif, en particulier sur le groupe des dépressions endogènes.

Au cours de recherches antérieures (en collaboration avec Selbach et Kanig), des modifications humorales caractéristiques et identiques dans leur forme étaient apparues lors du traitement des psychoses schizoïdes par la chlorpromazine, la

mépazine, la perazine et, assez paradoxalement, également par la réserpine. Il a paru intéressant, de ce fait, d'entreprendre des études correspondantes au cours de la pharmacothérapie des états dépressifs par le Tofrānil.

Des contrôles systématiques prolongés ont porté sur:

a) les érythrocytes;
b) les leucocytes;
c) les fractions protéiniques du sérum;
d) le taux des protéines sériques;
e) l'activité de la phosphatase alcaline dans le sérum.

En comparant les résultats de ces différents examens au point de vue statistique, on constate que:

1° Dans le groupe des psychoses schizoïdes, le fait le plus remarquable fut, par comparaison avec les cas normaux, une augmentation des α_2- et β-globulines sériques *avant* le début du traitement. La thérapie neuroleptique faisait régulièrement régresser ce taux.

Dans le syndrome dépressif, il n'y avait pas d'augmentation des α_2- et β-globulines *avant* le traitement au Tofrānil. L'effet de ce médicament a consisté dans une élévation passagère de leur taux, avec un maximum après la deuxième semaine.

2° Tant avec la phénothiazine qu'avec le Tofrānil, nous avons constaté une augmentation passagère significative de l'activité de la phosphatase alcaline dans le sérum, avec un maximum dans les 3e-5e semaines de traitement.

3° Le traitement au Tofrānil, comme celui à la chlorpromazine, provoque une éosinophilie relative et une augmentation du nombre des monocytes.

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ALTERATION OF THE CLINICAL PICTURE DURING TOFRĀNIL THERAPY*

MARCEL BERTHIAUME**

Our group has studied the effect of Tofrānil† on patients showing symptoms of transient or chronic depression, whatever the nature of their illness. No great improvement was expected, but in fact in a certain number of patients quite spectacular results were obtained which in our view demonstrate the undoubted value of this drug in the depressive states.

Six of the thirty patients studied in this series showed changes which are of interest whether regarded as improvements or as deteriorations. Each of these six cases will first be described in brief and the underlying pathology will then be discussed.

First case:

E. F., an unmarried woman teacher aged 35, had to enter hospital in July 1956 for psychic disturbances following an attack of jaundice in 1954. Since this attack she had been unable to follow her normal life, tended to wander away from her home, and complained of being spied upon and held up to ridicule. Unable to sleep, she alternated between periods of apathy and of agitation. The usual gamut of treatments resulted only in increasing apathy. In January 1958 she appeared to be in intense depression, and on February 22 Tofrānil was tried in a dose of 75 mg daily. On March 6 she became delirious to an extent never shown previously. Tofrānil given intra-muscularly merely increased the anxiety and delirium, which became extremely acute. The patient explained that the drug excited her, produced vague feelings of malaise and was the cause of her hallucinations.

Second case:

G. D., a single woman aged 23 admitted to hospital on October 3, 1955, showed on arrival paranoid tendencies, childish fantasies and above all a marked tendency to apathy. The illness started in 1953, when she became sullen and irritable, uninterested in work and inclined to violence when opposed. During her stay in hospital, where she received the usual treatment, she had several attacks of anxious depression. During one of these attacks in February 1958, Tofrānil was tried in doses of 75-225 mg daily for a total period of 3½ months. After some initial improvement the drug became ineffective and finally seemed to make the patient's anxiety worse, although it is possible that the drug was not actually responsible for this deterioration.

Third case:

I. B., a widow aged 34 without children, was admitted in June 1956 owing to psychotic reactions following the death of her husband. Despite two periods spent in the psychiatric wards of general hospitals, she was unable to take up her work again and found that her anxiety and agitation were becoming much worse. She also had depressive tendencies to the point of suicide, auditory hallucinations and a feeling of depersonalization.

After a stormy initial period she became increasingly calm and was able to leave in August 1956, only to return in the following December. Since then she has shown frequent exacerbations of anxious depression. Tofrānil was tried in February 1958 but seemed to aggravate her symptoms. Electro-convulsive therapy was also tried and effected an improvement, but the anxiety reappeared when she was again given Tofrānil. She claimed that the drug made her feel worse and affected her mouth.

*Translation.

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†Trade Mark.

Fourth case:

L. D., a married man aged 48 and a mechanic by trade, was admitted on October 8, 1958 because of depression for one year with a loss of weight of 60 lb. He had reached the stage of not eating or sleeping and of spending all his time in bed. He also showed considerable anxiety with an element of persecution but in the main appeared to be depressed, stating that he felt he was a Judas unworthy of living and that his wife was too good for him. In fact he twice attempted suicide. The present episode started in the autumn of 1957 following an influenzal attack which he took to be Asiatic influenza. He alleged, however, that his illness was connected with his trade (he repaired the looms of piece-work weavers) which he found exacting.

Following an examination which indicated involutional melancholia, Tofrānil was prescribed on October 16 in doses of 25 mg by mouth four times a day. On October 29 he had become overactive, somewhat euphoric, talkative and sleepless. He also complained of epigastric pain, ringing in the ears and headache. Tofrānil was reduced to 75 mg daily with pentobarbital at bedtime. On November 3 he was frankly hypomanic, and on the 4th he was found standing on the veranda railing with his head between a pipe and the ceiling. The possibility of attempted suicide was obvious but he maintained that he was acting the fool to make other people laugh. At this time it was discovered that the patient himself had stopped his treatment four or five days previously, having realized that it was exciting him. He also claimed that the drug burned his throat.

Fifth case:

M. G., a married man aged 43, formerly a postal worker, was admitted in October 1956, but his history showed disturbances of a paranoid nature which had been present for a long time. Since he resisted all forms of treatment he was transferred to an affiliated institution. He appears to have become increasingly preoccupied and depressed. On October 24, 1958 he was given 75 mg of Tofrānil daily. By November 1958 he had become markedly euphoric and several days later he invented an improbable story according to which he had been given permission by the authorities to remain indefinitely at home, or to return to the first institution if he had to be readmitted. The motive behind his story can easily be understood, although his behaviour was completely opposite to what it had been earlier.

Sixth case:

C. W., a bachelor aged 26, hemiplegic from birth and dysarthric, showed compensatory disturbances in his behaviour which necessitated his admission. He had a tendency to frequent bouts of depression with suicidal tendencies. During one of these bouts, on October 21, 1958, he was given Tofrānil at an initial dosage of 75 mg daily. He too became increasingly euphoric until after two months he fabricated a fantastic story which showed clear evidence of childish psychopathology. This story concerned marriage and a child by a young woman whom he had in actual fact met at his parents' home and knew to be remarried after a divorce. He had previously shown psychopathic episodes followed by bouts of depression but had never exhibited fantasies of this kind. The patient recognized and begged for his medication to be continued.

Conclusions

The changed symptoms described in these brief case histories are not specific to Tofrānil. They are familiar to the practising psychiatrist, being encountered especially during the use of stimulants and on occasion in electro-convulsive therapy. The point of interest is that they are produced by a drug classed as a sedative whose action was until now thought to be like that of chlorpromazine in

some respects. This similarity recalls that the tranquilizers also have occasional paradoxical effects. Our observations contain nothing new, having been reported by all workers interested in Tofrānil.

In four of our six patients (E. F., L. D., C. W. and M. G.) it appears that the drug caused disappearance of the inhibiting depressive element and hence allowed the underlying psychopathology to come into play, with development of euphoria in 3 patients only, E. F. having become stimulated but not euphoric. As has been shown so well by Sarwer-Foner, Azima and others, the psychological aspect and the personality structure are most important features in understanding the action of drugs.

In two other patients (G. D. and I. B.) the action is less clear. After Tofrānil had exerted a beneficial action at the start the anxiety became more acute, as if liberation from the inhibiting depression allowed its free manifestation. Nevertheless it is possible that the drug had no action and that the episode simply took its own course.

Three patients complained that the drug made them feel unwell. In L. D. this action did not modify in any way the euphoric element. E. F. showed an intensification of the delirious explosive element which was already present, while G. D.'s anxiety increased.

The literature throughout the ages records many explanations for these phenomena but they cannot be discussed here. However, we do consider that this stirring up of anxiety by drugs which inhibit depression represents a fairly common phenomenon in psychotherapy, namely an increase in anxiety brought about by the disappearance of a symptom at an inopportune moment. If this parallelism is established it suggests that when drugs are administered the accompanying psychopathological evolution should be borne in mind, so that undesirable secondary effects can be avoided.

Moreover, in patients showing a combination of depression and anxiety an increase of the latter is noted fairly often when depression has disappeared under treatment.

Although the pharmacological and physiological effects of Tofrānil are little understood at present, they are certainly important for an understanding of its action. This action was observed in only a limited number of our patients and may perhaps be due to a certain defect in excretion with resulting accumulation, or to some other metabolic disorder, but we have no evidence supporting this.

Résumé

Sur 30 patients atteints de dépression, et traités au Tofrānil, 6 ont présenté une modification de leurs symptômes semblable à celle qui apparaît parfois à la suite de la thérapie électroconvulsive ou après un traitement par les stimulants, et ceci bien que le Tofrānil soit généralement considéré comme ayant une action sédative.

Une explication possible de ce changement dans la symptomatologie serait l'inhibition de l'élément dépressif par le Tofrānil, ce qui permettrait à la psychopathologie sous-jacente de remonter à la surface. Trois de ces 6 malades ont présenté de l'euphorie, un autre de l'excitation sans euphorie; les deux derniers, après une amélioration initiale, ont vu leurs symptômes d'anxiété augmenter.

Du fait que ces modifications ne sont apparues que dans un nombre limité de cas, il se pourrait que la cause en soit une mauvaise élimination du remède, et son accumulation subséquente dans les tissus.

CONTROLLED ASSESSMENT OF ANTIDEPRESSANT DRUGS, INCLUDING TOFRĀNIL

J. W. Lovett Doust, D. J. Lewis, A. Miller, D. Sprott and R. L. D. Wright*

This investigation was set up under the auspices of the Drug Testing Committee of the University of Toronto Department of Psychiatry. Its aims included a clinical appraisal of Tofrānil† and an attempt to assess the anti-depressant effects of this drug under the most exacting circumstances conceivable, i.e. in a group of refractory, backward, chronically depressed patients each of whom had been shown previously to be unresponsive to all known treatment procedures. In the short time available for this presentation it will only be possible to mention some of the highlights of this work.

Let us consider first Stage I and the patients on whom we sought merely clinical impressions. To date there have been 40 of these, 25 being in-patients of the psychiatric division of a general hospital and the remainder depressed patients attending a Day Care Centre. In both locations we found Tofrānil a valuable means of relieving the depressive affect, providing the attending physician could take responsibility for any sequelae that occurred. The most alarming of the latter in our experience have been cardiovascular and of such a degree as to make the psychiatrist unwilling to treat the patient outside the hospital. Complete remission was shown by approximately one-third of the cases, some improvement in another third and no effect in the remainder. Best results were seen in endogenous, postpartum, involutional and senile depressions, reactive and neurotic disorders being the least affected.

Stage II of the investigation was concerned with a scientific study of the effect of Tofrānil in our refractory group of patients. An experimental design was worked out calling for replications in groups of four, on the basis of a modified Latin square. Involved were 24 carefully selected, therapeutically recalcitrant, cooperative, chronically depressed patients. Comparison effects were sought in these patients from the administration of: no drug, a placebo, dextro-amphetamine, iproniazid, and Tofrānil. A double-blind procedure was used and each drug and the placebo were disguised by emplacement within identical orange gelatin capsules. Dosage was held constant and set at approximately the safe maximum for each drug. In the case of Tofrānil, this was 200 mg per diem given in four divided doses through the day. Timing was arranged so that each drug was continued sufficiently long to enable its maximum therapeutic effects to be attained, while a drug-free interval was interposed between each of a duration corresponding to the expected time of its excretion. For Tofrānil, these periods were four weeks and one week respectively. In accordance with the statistical design, in each group of four patients each drug was preceded by every other drug once and once only. All patients were appraised daily by the same clinical psychiatrist and specially trained research nurse and were tested weekly by the research psychologist, whether or not they happened actually to be receiving a drug at the time. The changes brought about by the initial dry run, the placebo and the three anti-depressant drugs were monitored by two behavioral rating scales (the Lehmann Depression scale and one devised by us), and by the measurement of a number of psychophysiologic functions selected in the hope that they would reflect affective responses in the patient, or at least correlate with such responses. In all, some 50 measurements were taken, based on 8 separate

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monitoring devices. The latter included audio-visual reaction time, maximal tapping speed, critical flicker fusion thresholds, estimation of filled and empty time, and tests of foresight, motor skill and ability to profit from experience. In addition, we attempted to gain an objective assessment of behavioural change through the analysis of motion picture records taken from a camera hidden from the patient's view and through a count of the depressive content of the patient's utterances at discreet times during the test procedures. Aside from such effects, the clinical staff were responsible for daily blood pressures, thrice daily body temperatures, notation of eating and sleeping habits, etc., while the laboratory staff reported regularly on blood and urine specimens.

Interim Statement of Results

A. *Statistical.* Complete statistical analysis of the rating scales and monitors has not yet been accomplished. However, we may state that none of the three drugs or placebo exerted marked, predictable, clinical effects on our group of 24 patients taken as a whole. It is not impossible that some statistically significant effects may be found among the rating scales and monitors, but these would not be marked enough to constitute clinically significant effects.

B. *Clinical.* Individual reactions to the drugs varied widely, as one might expect from the diversity of patients included in the investigation. Two subjects improved dramatically to the point where discharge would be possible were their Tofrānil medication continued. Two more improved also on Tofrānil but could not be considered for discharge for physical reasons quite unrelated to the depressive features of their illness. One subject was ready for discharge after three weeks on iproniazid, and it is probable that she would have responded similarly to Tofrānil. The four patients most helped by Tofrānil were characteristically unresponsive to other known treatments, including previously administered ECT. A further two

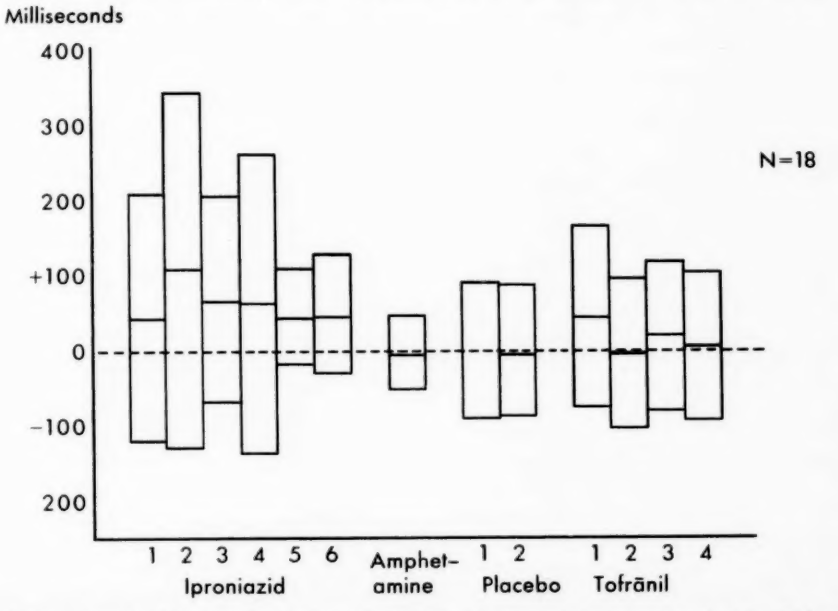

Fig. 1. Means & SD's of reaction times under experimental drugs, relative to pre-drug baseline. Tofrānil does not significantly change group audio-visual reaction time; iproniazid increases it.

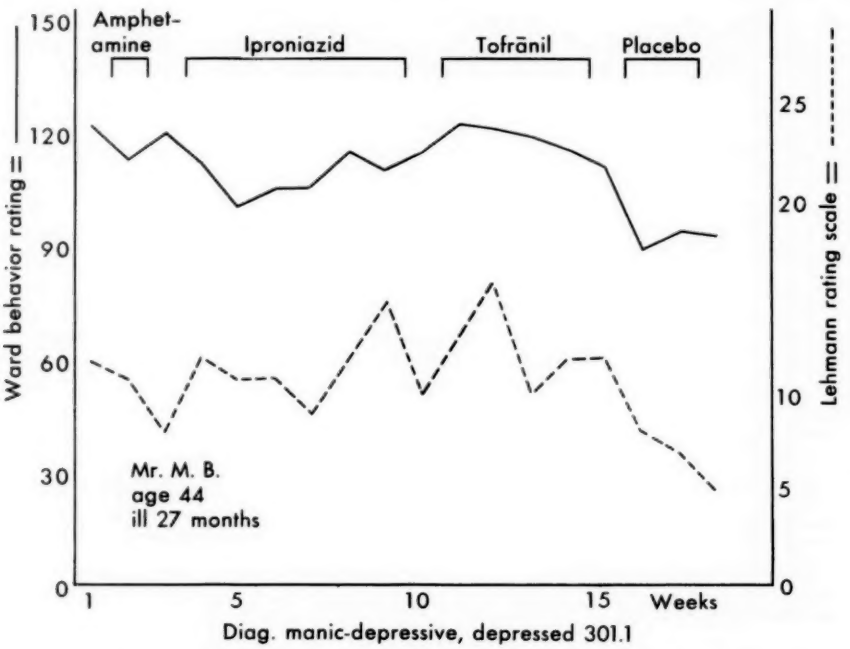

Fig. 2. Individual failure to respond to any drug or placebo (by rating scales).

patients were probably improved by Tofrānil in that their subjective depression lifted, but this mood change was accompanied by violent behaviour necessitating removal to a disturbed ward. Another two patients were similarly affected by iproniazid, and it is possible that this freeing of the patient from involutional controls may cause antisocial behavior of even more severe degree to emerge in cases where basic personality aberrations are held in check by depressive affect. One severely depressed woman became worse with each drug in turn, and finally had to be given over to ECT. Two elderly men, both arteriosclerotic, were tried briefly on iproniazid and Tofrānil in turn, but had to be taken off because of dangerous hypotensive seizures, and contributed no data to the project. Another elderly man with advanced coronary artery disease who was acutely confused and depressed may have been helped slightly by Tofrānil but became distinctly worse when transferred to the succeeding drugs and was given ECT. One young man improved slightly on Tofrānil, relapsed on the other drugs, and then was taken off the drug programme to undergo a lithotomy; several days following this his mental condition cleared up entirely and he was discharged. Ten patients were not apparently helped to any great extent by any of the four drugs, but did not show complications or further worsening either. The effect of serial administration of the drugs is still unclear, but it may be stated fairly confidently that there is no general rule. Frequently improvement on one drug would be continued or accelerated on the next, but there were marked exceptions in which the opposite was true.

Figure 1 illustrates the group effects of placebo and experimental drugs on one monitor, the audio-visual reaction time. No significant influence was observed as a result of the administration of dextro-amphetamine or of Tofrānil, the results of which equalled those of the placebo; the influence of iproniazid was, however,

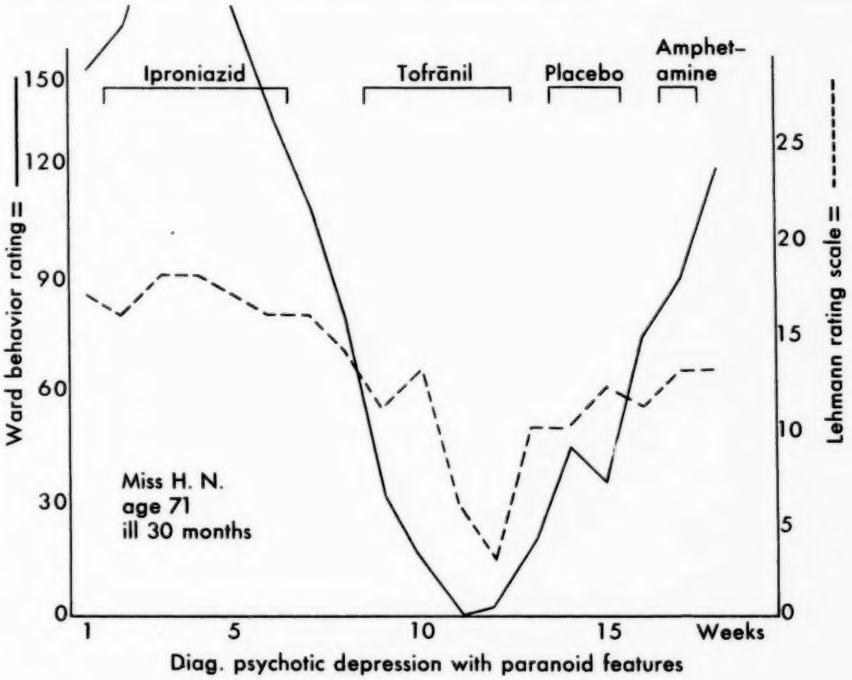

Fig. 3. Excellent individual response to Tofrānil coupled with worsening when dextro-amphetamine and iproniazid are administered (by rating scales).

significantly to increase reaction time. Figures 2 and 3 exemplify the relative success (or lack of it) of each drug in two individual patients, as monitored by the Lehmann Depression scale and by our DRU behavioural rating scale. In Figure 2 complete drug resistance is seen in a male manic-depressive aged 44, while the therapeutic influence of Tofrānil is compared dramatically in Figure 3 with the impotence of iproniazid, dextro-amphetamine and the placebo in an elderly female with paranoid depression.

Résumé

Les auteurs relatent les résultats de deux séries de recherches, touchant les effets du Tofrānil. La première série comportait un essai clinique sur un groupe de 40 patients, pris dans la division de psychiatrie d'un hôpital général et dans une consultation policlinique. Le médicament est précieux dans les cas où un électrochoc est contre-indiqué. Tant dans la policlinique qu'à l'hôpital, les résultats ont été meilleurs dans les psychoses endogènes que dans les dépressions névrotiques psychoréactives, mais l'usage prolongé de cette médication a été cause d'effets biochimiques secondaires désagréables, et parfois alarmants.

Dans la seconde série, on a tenté une évaluation plus rigoureuse et plus scientifique du Tofrānil, en utilisant un schéma expérimental formel, deux échelles d'appréciation indépendantes, et des mesures objectives d'un certain nombre de fonctions psychophysiologiques, régulièrement répétées. Ce programme comportait un test croisé à double effet, soit la comparaison entre l'action du Tofrānil et celle de deux autres médicaments antidépressifs et d'un placebo; chez un groupe hétérogène de

patients hospitalisés depuis longtemps, et dont le seul caractère commun était la présence d'un état dépressif et son irréversibilité, prouvée par l'échec d'autres formes adéquates de traitement. La répartition des patients par groupes de 4, que l'on pouvait mélanger de six manières différentes, permettait d'analyser chez le même patient l'effet des divers médicaments et celui des placebos, et de faire la comparaison avec des périodes sans administration de remèdes. Dans chaque groupe de quatre, les sujets recevaient médicaments et placebos chacun dans un ordre différent. L'amphétamine et l'iproniazide ont été choisis comme substances de comparaison, et administrés à la dose maximum compatible avec l'innocuité, dans des encapsulages identiques. Les résultats de ces expériences sont encore en cours d'examen. Provisoirement, nous pouvons dire qu'aucun de ces cas réfractaires ne s'est trouvé guéri par l'un ou par l'autre des trois antidépressifs. Cependant une amélioration a été notée dans les signes cliniques et dans certaines des épreuves psychophysiologiques chez plusieurs d'entre eux, tant par l'effet de l'iproniazide, que par celui du Tofrānil.

General discussion from the floor (summarized)

Dr. Doust was asked whether one week on a drug is long enough for adequate study, since the drug may remain in the tissues for a longer period of time. In reply, the author explained that the length of time a patient remained on the drug in a controlled experiment was decided on the basis of the excretion pattern of the drug. Thus, four to six weeks are necessary in the case of iproniazid but only one week is sufficient for Tofrānil.

BASIC DYNAMIC STATES IN ENDOGENOUS PSYCHOSES, WITH SPECIAL REFERENCE TO THE PHARMACOTHERAPY OF DEPRESSIVE STATES*

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The consistent diagnosis of endogenous psychoses, which under Kraepelin's influence seemed to have been achieved around the turn of the century, has now become lost again after only a few decades. Only Kraepelin's dichotomy (1) which established a distinction in the field of endogenous psychoses between dementia praecox and manic depressive psychoses remains valid. Most of what appeared to be scientifically sound, however, has again become doubtful: relativity in the concept of "endogenous;" the difficulty of making a clear distinction between the two entities; the unreliability of all systems of classification so far attempted. Controversies which at first were mostly concerned with schizophrenic psychoses have been extended since the second world war to the realm of depressive psychoses. New forms have been described, such as Schneider's "Untergrunddepression" (2), López Ibor's "anxiety thymopathy" (3), Weitbrecht's "endo-reactive dysthymia" (4). The part played by reactive and somatic factors in endogenous depressive states has been thoroughly investigated, particularly in central Europe where the recent catastrophic experiences have provided valuable opportunities for study. As to the nosology of endogenous psychoses, decades of argument have not resulted in agreement, only in agreement to differ. It is questionable whether there is in fact any point in arguing about the classification of endogenous psychoses. The most varied endogenous states can be described from the course of the disease and from their psychopathologic symptomatology. Whether different diseases and different pathologic groups are really being described remains very doubtful.

A critical assessment of the present state of our knowledge suggests that we should elevate to a heuristic principle the abandonment of any nosology of endogenous psychoses, and return, as other present-day workers have done, in particular Ey (5), to a unified concept of psychosis. Of course, we no longer believe that depression and mania, "insanity" and "idiocy," are stages of one and the same process and normally develop one from the other. Nevertheless, in our opinion, it would be extremely useful to regard endogenous psychoses in principle as a single phenomenon and to seek initially within this unit, not a diagnosis, but rather a range of broad psychopathological types. A similar tendency appears in Freyhan's (6) efforts, a kind of "double-entry bookkeeping," to base therapy on "target symptoms" rather than on diagnosis. We regard endogenous psychoses basically as disturbances of psychic dynamics, as changes occurring primarily in the sphere of emotion and intent which only from this point on affect the personality. If it were possible to characterize the psychopathological picture by the specific nature of the fundamental dynamic disorder, the therapy of psychoses would be greatly helped, since the somatic methods of treatment, and particularly the psychotropic drugs, appear mainly to affect the psychic dynamics.

Elsewhere (9) we have attempted to describe four basic dynamic states and to use them to distinguish different types of endogenous psychoses. These are:

1. Dynamic *reduction*. This is characterized by impoverishment, narrowing and loss of flexibility of the psychic dynamics. As a fundamental state it is found mainly in depressive psychoses.

2. Dynamic *expansion*, expressing itself in loosening, freeing and heightening of the dynamic process in *manic* psychoses.

*Translation.

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3. Dynamic *unsteadiness* found in *acute schizophrenic* psychoses.

4. Dynamic *emptying* as a general dynamic insufficiency in *defective schizophrenic* psychoses.

It is beyond the scope of this article to describe in detail these fundamental states, which in specific cases may overlap and occur concurrently. We shall limit ourselves to discussing the consequences of this dynamistic concept for the pharmacotherapy of psychoses.

The introduction of chlorpromazine and reserpine may be regarded as marking the beginning of the effective pharmacotherapy of endogenous psychoses. At that time only the *thymoplegic* principle (7-9) was available. The action of these two drugs (10, 11) is stabilizing and suppressive in the emotional-intentional sphere. From the dynamistic point of view, the effectiveness of thymoplegic therapy has been found to be quite independent of the diagnosis. The more agitated the psychosis, the more successful is the treatment likely to be, whether the condition is one of a manic or of an acute schizophrenic nature. Even some agitated depressions may be influenced up to a point, whereas the majority of depressions and the bland schizophrenic disorders are hardly affected by the treatment. Regardless of the diagnostic classification, the thymoplegic principle acts wherever the salient feature is a raising of the dynamic level or an excitation of unsteadiness of the dynamic process. We are mainly indebted to C. and H. Selbach (12) for a somatological explanation of this state of affairs.

With the introduction of iproniazid and Tofrānil* we have examples of a quite different therapeutic principle, one which—like convulsive therapy—makes possible a continuous activation of the psychic dynamics. Differences in the mode of action of the two drugs are shown by the fact that iproniazid has an activating and stimulating effect even on normal persons, whereas Tofrānil develops its thymoleptic action (13) when the dynamic level is lowered. As shown by the extensive studies of Schmitt with Tofrānil (14) and also by our own work with both Tofrānil and iproniazid, the patients most readily responsive are those suffering from inhibitional vital depressions. We have also been successful in cases of dynamic emptying, in bland schizophrenias and even in adynamic non-psychotic states of exhaustion and depressive moods. If the initial dynamic state is ignored, surprising results may be observed when an activating therapeutic drug is used: schizophrenic psychoses may suddenly flare up again, depressed patients may become more agitated; in cases of agitated involutional depression neither previously nor subsequently schizophrenic, delusions or even acoustic hallucinations may be caused, as we have found with iproniazid. Our first impression is that Tofrānil has a more continuous, less "thymeretic" effect; it is clearly less likely than iproniazid to produce "atypical" symptoms. We would like to stress once more that in pharmacotherapy it is not the diagnosis which is decisive but the character of the fundamental dynamic process.

The view that thymoleptics represent something entirely new in the pharmacotherapy of depressive psychoses is opposed by the fact that the analeptic amines, in spite of their known action, have failed in the treatment of depressions. But it is just this fact which points clearly to the primary effect in the pharmacotherapy of psychoses: the therapeutic effectiveness of both thymoplegics and thymoleptics depends mainly on their capacity to *stabilize* the dynamic process and to lower or raise the energetic level permanently. Of particular significance, furthermore, is the direct action of thymotropic substances on *emotivity*, an action which the analeptic amines do not possess. In the development of new psychotherapeutic drugs, preference should be given to substances having an elective *thymotropic* effect yet acting with sufficient continuity to achieve a consolidation of the dynamic process

*Trade Mark.

at the desired therapeutic level. We already have a sufficiency of thymoplegics. There are good grounds for the hope that we are only at the beginning of the development of thymoleptic drugs and above all of the pharmacotherapy of depressive psychoses.

Résumé

La classification des psychoses endogènes s'entoure de tant de complexité et de controverse qu'il vaut mieux les reconsidérer comme étant des formes psychopathologiques variées d'un seul phénomène. Ces formes peuvent être classifiées dynamiquement en quatre classes: réduction dynamique, expansion dynamique, instabilité dynamique, et insuffisance dynamique. En fonction de ces états dynamiques, on décrit l'effet de différents médicaments sur les psychoses endogènes, et l'action spécifique du Tofrānil est comparée d'une part avec celle d'agents thymoplégiques (chlorpromazine et réserpine), et d'autre part avec celle de l'iproniazide. Il semble que Tofrānil, dans les cas de psychoses endogènes, comparé à l'iproniazide est moins susceptible de produire des symptômes atypiques.

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